**IN THE UNITED STATES DISTRICT COURT FOR THE DISTRICT OF NEW JERSEY**

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| IN RE: JOHNSON & JOHNSON TALCUM POWDER PRODUCTS MARKETING, SALES PRACTICES AND PRODUCTS LIABILITY LITIGATION | ) | MDL Docket No. 2738 |
| This Document Relates To All Cases | ) | |

**DEFENDANTS JOHNSON & JOHNSON AND JOHNSON & JOHNSON CONSUMER INC.'S MEMORANDUM OF LAW IN SUPPORT OF MOTION TO EXCLUDE PLAINTIFFS' EXPERTS' GENERAL CAUSATION OPINIONS**

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Plaintiffs' experts' general causation opinions are methodologically unsound and should be excluded under *Daubert* because they misapply scientific principles, engage in unsupported leaps of logic, and distort epidemiology in a results-oriented manner that transforms an important tool for advancing public health into an unprincipled weapon for litigation.[1]

Throughout their reports, plaintiffs' experts declare that a "strong" association exists between perineal talc use and ovarian cancer,[2] when all epidemiological evidence is to the contrary.[3] They assert that there is "consistent"

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[1] This motion seeks to exclude the opinions of the following witnesses in their entirety: Arch Carson, Daniel Clarke-Pearson, Sarah Kane, Anne McTiernan, Patricia Moorman, Jack Siemiatycki, Sonal Singh, Ellen Blair Smith, Rebecca Smith-Bindman and Judith Wolf. It also seeks to exclude Laura Plunkett's opinions in part (Expert Report of Laura Plunkett, Ph.D., D.A.B.T. ("Plunkett Rep.") at 48-52, 77, Nov. 16, 2018) (attached as Ex. C28 to Certification of Julie Tersigni, Esq. ("Tersigni Cert.")))), even though she attempted to disclaim offering a general causation opinion at her deposition (*see* Dep. of Laura Plunkett, Ph.D., D.A.B.T. 33:22-34:1, Dec. 19, 2018 (attached as Ex. B33 to Tersigni Cert.)).

[2] (*E.g.*, Expert Report of Rebecca Smith-Bindman, M.D. ("Smith-Bindman Rep.") at 37, Nov. 15, 2018 (attached as Ex. C36 to Tersigni Cert.) ("extremely strong"); Expert Report of Ellen Blair Smith, M.D. ("Smith Rep.") at 19, Nov. 16, 2018 (attached as Ex. C16 to Tersigni Cert.) ("significant" association); Expert Report of Jack Siemiatycki, M.Sc., Ph.D. ("Siemiatycki Rep.") at 63, Nov. 16, 2018 (attached as Ex. C21 to Tersigni Cert.) ("high" risk); Expert Report of Sonal Singh, M.D., M.P.H. ("Singh Rep.") at 63, Nov. 16, 2018 (attached as Ex. C40 to Tersigni Cert.) ("strong").)

[3] *E.g.*, Int'l Agency for Research on Cancer, World Health Org., 93 *Monographs on the Evaluation of Carcinogenic Risks to Humans: Carbon Black, Titanium Dioxide, and Talc* 277, 411-13 (2010) ("IARC 2010 Monograph") (attached as Ex. A72 to Tersigni Cert.) ("modest" elevation in risk).

evidence of such an association across the literature,[4] even though the results of the relevant epidemiological studies vary by study design.[5] They insist that there is "convincing" evidence of a dose-response relationship between talc use and ovarian cancer,[6] even though the scientific evidence is "inconsistent" with respect to dose-response.[7] And they claim that there is "compelling" evidence of a

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[4] (*E.g.*, Smith-Bindman Rep. at 38 ("highly consistent"); Smith Rep. at 20 ("impressive" consistency); Siemiatycki Rep. at 64 ("consistently elevated risk"); Singh Rep. at 63 ("generally consistent").)

[5] Nat'l Cancer Inst., *Ovarian, Fallopian Tube, and Primary Peritoneal Cancer Prevention (PDQ®)–Health Professional Version*, https://www.cancer.gov/types/ovarian/hp/ovarian-prevention-pdq (last updated Mar. 1, 2019) ("2019 NCI PDQ") (attached as Ex. A104 to Tersigni Cert.) (concluding the "weight of evidence does not support an association between perineal talc exposure and increased risk of ovarian cancer" and noting, among other things, the "[r]esults from case-control and cohort studies are inconsistent"); Berge et al., *Genital use of talc and risk of ovarian cancer: a meta-analysis*, 27(3) Eur J Cancer Prev. 248 (2018) (attached as Ex. A11 to Tersigni Cert.) ("Berge 2018") (noting that "[t]he fact that the association between genital talc use and risk of ovarian cancer is present in case-control, but not in cohort studies, can be attributed to bias in the former type of studies").

[6] (*E.g.*, Expert Report of Anne McTiernan, M.D., Ph.D. ("McTiernan Rep.") at 66, Nov. 16, 2018 (attached as Ex. C7 to Tersigni Cert.) ("placed significant weight" on dose-response evidence); Expert Report of Arch Carson, M.D., Ph.D. ("Carson Rep.") at 9, Nov. 16, 2018 (attached as Ex. C9 to Tersigni Cert.) ("clear dose response"); Expert Report of Daniel L. Clarke-Pearson, M.D. ("Clarke-Pearson Rep.") at 9, Nov. 16, 2018 (attached as Ex. C14 to Tersigni Cert.) ("anticipate[s]" that dose-response evidence will become stronger); Siemiatycki Rep. at 63 ("clear indication" of dose-response in preferred studies).)

[7] IARC 2010 Monograph at 411-13; Terry et al., *Genital Powder Use and Risk of Ovarian Cancer: A Pooled Analysis of 8,525 Cases and 9,859 Controls*, 6(8) Cancer Prevention Res. 811, 811 (abstract) (2013) ("Terry 2013") (attached as

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mechanism by which talc can cause ovarian cancer,[8] even though the very documents on which they rely have concluded that evidence of mechanism is "insufficient" and that a specific mechanism has "not been identified."[9] These opinions do not "reliably flow from the facts known to the expert[s] and the methodology used," and instead "fly in the face of reality." *In re TMI Litig.*, 193 F.3d 613, 683 (3d Cir. 1999), *amended in nonmaterial part*, 199 F.3d 158 (3d Cir. 2000) (citation omitted). In a nutshell, this is science for the courtroom, not science for the laboratory.

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Ex. A139 to Tersigni Cert.) ("Whether risk increases with number of genital powder applications and for all histologic types of ovarian cancer also ***remains uncertain*** . . . . Among genital powder users, we observed ***no significant trend in risk with increasing number of lifetime applications***.") (emphasis added).

[8] (*E.g.*, Smith Rep. at 20 ("compelling"); Expert Report of Judith Zelikoff, Ph.D. ("Zelikoff Rep.") at 8, Nov. 16, 2018 (attached as Ex. C24 to Tersigni Cert.) ("substantial evidence"); Expert Report of Patricia G. Moorman, M.S.P.H., Ph.D. ("Moorman Rep.") at 37, Nov. 16, 2018 (attached as Ex. C35 to Tersigni Cert.) ("persuasive"); Singh Rep. at 65 ("highly . . . plausible"); Smith-Bindman Rep. at 13 ("very strong").)

[9] *See* Health Canada, Draft Screening Assessment: Talc ($Mg_3H_2(SiO_3)_4$) (Chem. Abstracts Serv. Registry No. 14807-96-6) ("Draft Screening Assessment") at 21 (2018) (emphasis added) (attached as Ex. A58 to Tersigni Cert.); Penninkilampi & Eslick, *Perineal Talc Use and Ovarian Cancer: A Systematic Review and Meta-Analysis*, 29 Epidemiology 41, 45 (2018) ("Penninkilampi 2018") (attached as Ex. A109 to Tersigni Cert.) (cited by all 11 experts whose opinions are subject to this memorandum).

Two separate state courts in other talc litigation proceedings have already looked at similar opinions and thrown them out as unreliable. In New Jersey, the trial court overseeing statewide talc proceedings excluded the causation opinions of two plaintiffs' experts espousing the same theories as scientifically invalid. *See Carl v. Johnson & Johnson*, Nos. ATL-L-6546-14, ATL-L-6540-14, 2016 WL 4580145, at *19 (N.J. Super. Ct. Law Div. Sept. 2, 2016), *appeal pending*. And the court overseeing similar proceedings in California ultimately reached the same conclusion, deciding after a jury had awarded a plaintiff $417 million that the verdict could not stand "given the lack of anything other than a hypothesis about causation and the nature of the epidemiological evidence presented." *In re Johnson & Johnson Talcum Powder Cases*, No. BC628228, 2017 WL 4780572, at *19, *25 (Cal. Super. Ct. Oct. 20, 2017), *appeal pending*. This Court should reach the same conclusions for several reasons.

***First***, while plaintiffs' experts claim that they undertook causation analyses using the "Bradford Hill" factors (a framework used by scientists to determine whether epidemiological associations are indicative of causation), their methodologies and analyses were flawed at virtually every step. Most notably:

- ***The data do not show a strong association.*** It is well accepted that the claimed association between talc and ovarian cancer is either nonexistent or too weak to show causation, a conclusion that has been confirmed by recent large and well-designed prospective studies, as well as governmental organizations. This weak association is particularly suspect because it may well be the result of recall bias (essentially, the

propensity for study participants to over-report past talc use), as demonstrated in a recent talc study co-authored by plaintiffs' own expert, Dr. Moorman.[10] There is also a significant concern about confounding because the case-control studies did not consistently adjust for potential ovarian cancer risk factors. For example, a recent study found that women who used talc were more likely to douche, and that douching almost doubled incidences of ovarian cancer, while talc use alone did not show an elevated risk.[11] Virtually none of the prior talc studies adjusted for douching, and studies have failed to control uniformly for many other confounding factors as well, calling their results into further question.

- ***The data do not consistently show an association.*** Cohort studies do not show an increased risk of ovarian cancer with talc use, while only a subset of case-control studies do. This fact, by itself, compels a conclusion that the data are inconsistent, a conclusion that plaintiffs' experts are able to dispute only by brushing aside the literature with which they do not agree. Although plaintiffs' experts proffer endless speculation as to why the talc cohort studies might be flawed, they do not apply their criticisms even-handedly to case-control studies, which are widely recognized to have significant limitations. And plaintiffs' attack on the long-established concept of statistical significance highlights their willingness to buck the scientific consensus in order to reach their desired results.

- ***There is no dose-response relationship.*** The literature is replete with statements that no consistent dose-response relationship has been demonstrated between talc use and ovarian cancer, which is significant because a fundamental tenet of epidemiology is that a disease-causing agent should pose greater risks of disease at higher doses. As defendants' expert Dr. Christian Merlo explained, studies of dose-

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[10] Schildkraut et al., *Association between Body Powder Use and Ovarian Cancer: The African American Cancer Epidemiology Study*, 25(10) Cancer Epidemiology, Biomarkers & Prevention 1411, 1415 (2016) ("Schildkraut 2016") (attached as Ex. A129 to Tersigni Cert.).

[11] Gonzalez et al., *Douching, Talc Use, and Risk of Ovarian Cancer*, 27(6) Epidemiology 797 (2016) ("Gonzalez 2016") (attached as Ex. A47 to Tersigni Cert.).

response have been all over the map – finding "(1) random or 'sine wave' (up and down) risk; (2) convex (up then down) risk; (3) concave (down then up) risk; and (4) even decreasing risk" – a random pattern of results that "is a red flag to epidemiologists" evaluating study data.[12] "Moreover, study authors and plaintiffs' experts all agree that there are major challenges to interpreting the study findings on dose-response because there can be no assurance that any estimates of talc use are accurate or valid," since there is no way to measure how much talc a woman uses (let alone, how much – if any – actually enters the body).[13]

- ***The remaining Bradford Hill factors do not support causation.*** There is no plausible biological mechanism of injury (as discussed in more detail in defendants' separate memorandum addressing biological plausibility); plaintiffs' experts' theory is not supported by experimental evidence; and it is incoherent with broader scientific knowledge, including the knowledge that genetic mutations are the established cause of cancer and that talc does not cause mutations. Plaintiffs' experts' opinions also fail to grapple with the improbability that talc exposure causes all (or even most) of the various different subtypes of ovarian cancer, which are essentially different diseases with different suspected etiologies.

***Second***, plaintiffs have separately attempted to show that talc use causes high-grade serous ovarian cancer ("HGSOC") – one of many diverse subtypes of ovarian cancer – through a flawed "systematic meta-analytic review" conducted by Dr. Smith-Bindman. But Dr. Smith-Bindman's analysis is methodologically flawed and patently unreliable. Dr. Smith-Bindman reviewed the larger body of literature first and then analyzed particular subsets of data from prior cherry-picked

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[12] (Expert Report of Christian Merlo, M.D., M.P.H. ("Merlo Rep.") at 32, Feb. 25, 2019 (attached as Ex. C13 to Tersigni Cert.).)

[13] (Expert Report of Gregory Diette, M.D., M.H.S. ("Diette Rep.") at 3, Feb. 25, 2019 (attached as Ex. C18 to Tersigni Cert.).)

studies in order to "prove" her pre-conceived thesis. This is known as a "post-hoc subgroup analysis," a practice that is strongly frowned upon by the epidemiologic community as unreliable. And Dr. Smith-Bindman's analysis was all the more unreliable because she used subjective, inconsistent inclusion and exclusion criteria, as well as inaccurate data, in assessing the body of epidemiologic literature.

***Third***, plaintiffs' experts' opinions are independently unreliable because they contradict the overwhelming consensus that there is insufficient evidence of a causal association. Among other bodies, the International Agency for Research on Cancer ("IARC"), the National Cancer Institute ("NCI") and the U.S. Food and Drug Administration ("FDA") have concluded that existing science does not support the conclusion that talc is a cause of ovarian cancer.[14] And a review article published in March in the *New England Journal of Medicine* (considered the top journal in the world) identified risk factors for two prominent subtypes of ovarian

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[14] *See* IARC 2010 Monograph at 411-13; 2019 NCI PDQ; Letter from Steven M. Musser, Ph.D., Deputy Dir. for Sci. Operations, Ctr. for Food Safety & Applied Nutrition, to Samuel S. Epstein, M.D., Cancer Prev. Coalition, Univ. of Ill. – Chi. School of Pub. Health, at 4-5 (Apr. 1, 2014) ("FDA Denial Letter") (attached as Ex. A89 to Tersigni Cert.). Plaintiffs' counsel and their experts rely heavily on various statements in a recent Draft Screening Assessment of talc by Health Canada, but its bottom-line conclusion does not go further than prior regulatory pronouncements, proposing only that a "***potential*** concern for human health has been identified" in connection with perineal talc use. Draft Screening Assessment at iii (emphasis added).

cancer, but like numerous other reviews, ***did not list talc use***.[15] Plaintiffs are thus asking this Court to overrule the scientific consensus and declare that law knows better than science. Even two of plaintiffs' experts (Siemiatycki and Moorman) recognized in their pre-litigation peer-reviewed publications that the evidence is insufficient to establish causation. The fact that these two experts have now changed their tune is one more reason to exclude their opinions from trial, especially because Dr. Moorman has frankly admitted that she only holds her causation opinion for purposes of litigation and would not assert it in her scientific work.

For all of these reasons, discussed in more detail below, plaintiffs' experts' general causation opinions should be excluded under *Daubert.*

## BACKGROUND

The question whether talc use causes ovarian cancer has been investigated for ***nearly half a century***, and in that time, there have been more than 30 observational studies, numerous meta-analyses and several experimental studies published on the issue. None of these studies purports to have established a causal link between talc use and ovarian cancer; nor has the scientific community taken this position. Nevertheless, plaintiffs' experts assert in unison that the scientific

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[15] *See* Morice et al., *Mucinous Ovarian Carcinoma*, 380(13) N. Engl. J. Med. 1256 (2019) ("Morice 2019") (attached as Ex. A96 to Tersigni Cert.).

evidence has established that talc use causes ovarian cancer. These opinions are based on an inherently unreliable and unscientific interpretation of the relevant literature that improperly elevates the importance of studies that are prone to bias and confounding over those that are generally deemed more reliable by the scientific community.

## A. Fundamental Epidemiologic Principles

### 1. The Hierarchy Of Scientific Evidence

The "hierarchy of evidence" is a long-standing, well-established principle in the epidemiological community for weighing clinical and observational studies.[16]

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[16] *See, e.g.*, Center for Evidence-Based Management, *What are the levels of evidence?*, https://www.cebma.org/faq/what-are-the-levels-of-evidence/ (last visited May 1, 2019) (attached as Ex. A19 to Tersigni Cert.); Green et al., Fed. Judicial Ctr., *Reference Guide on Epidemiology*, *in Reference Manual on Scientific Evidence* 549, 723-24 (3d ed. 2011) (attached as Ex. A51 to Tersigni Cert.) ("Epidemiology Reference Manual"); World Cancer Res. Fund & Am. Inst. for Cancer Res., *Continuous Update Project Expert Report: Judging the Evidence* at 7 (2018) (attached as Ex. A153 to Tersigni Cert.) (panel Dr. McTiernan serves on explaining that "[t]he hierarchy of epidemiological evidence places cohort studies above case-control studies" and that "[c]ohort studies are likely to be the main source of evidence" due in part to their prospective design); Langseth et al., *Perineal Use of Talc and Risk of Ovarian Cancer*, 62 J. Epidemiology & Cmty. Health 358, 358 (2008) (attached as Ex. A88 to Tersigni Cert.) ("Langseth 2008") (study co-written by Dr. Siemiatycki explaining that a talc cohort study was "arguably the strongest study because of its partly prospective ascertainment of exposure" and conversely, that "the influence of . . . recall bias cannot be ruled out" in case-control studies); *Carl*, 2016 WL 4580145, at *12, *19 (case-control studies "are considered less reliable than a prospective cohort study"); *Planned Parenthood Fed'n of Am. v. Ashcroft*, 320 F. Supp. 2d 957, 985 (N.D. Cal. 2004) (recognizing that "[r]esearch methodology is evaluated on a hierarchy," with

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Randomized clinical trials – wherein study participants are randomly assigned to a particular intervention or exposure and followed prospectively for the outcome of interest – are generally viewed as providing the strongest evidence to support a causal relationship between an exposure and an outcome in light of their lack of susceptibility to bias.[17]

Randomized clinical trials are followed by "observational" studies, which include – in descending order of reliability – cohort studies, case-control studies and cross-sectional studies.[18] Observational studies examine the incidence, distribution and causes of disease in human populations.[19] The difference between cohort and case-control studies relates to design. Cohort studies are prospective: they begin by identifying a large group of healthy women and follow them forward in time with regard to the agent and disease at issue. Case-control studies, by contrast, are retrospective: they compare a group of women already diagnosed

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prospective studies ranking above retrospective studies), *aff'd sub nom. Planned Parenthood Fed'n of Am., Inc. v. Gonzales*, 435 F.3d 1163 (9th Cir. 2006), *rev'd on other grounds sub nom. Gonzales v. Carhart*, 550 U.S 124 (2007). (*See generally* Expert Report of Kevin Holcomb, M.D., F.A.C.O.G. ("Holcomb Rep.") at 8, Feb. 25, 2019 (attached as Ex. C27 to Tersigni Cert.); Merlo Rep. at 35.)

17 *See, e.g.*, Center for Evidence-Based Management, *What are the levels of evidence?*, https://www.cebma.org/faq/what-are-the-levels-of-evidence/.

18 *Id.*

19 *See* Epidemiology Reference Manual at 551.

with ovarian cancer (cases) to a matched group of women without the disease (controls) and attempt to compare risk based on both groups' recollection of their past talc use.

Cohort studies are "widely regarded as more reliable than retrospective case-control studies because they are not susceptible to recall bias, which is the propensity of participants with the disease that is being studied to inaccurately report their exposure to the agent at issue, a phenomenon that can generate inflated risk estimates."[20]

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[20] (Diette Rep. at 5; *see also* Holcomb Rep. at 8-9; Merlo Rep. at 36; *see also* Dep. of Patricia G. Moorman, M.S.P.H., Ph.D. ("Moorman Dep.") 301:21-302:4, Jan. 25, 2019 (attached as Ex. B39 to Tersigni Cert.) ("typically, the cohort study is ranked as a stronger study design"); Smith-Bindman Rep. at 16 ("The commonly held view is that cohort studies are better than case-control studies.").) Notwithstanding these concessions, plaintiffs' counsel challenged the accepted view that cohort studies generally offer higher quality evidence than case-control studies at depositions of several defendants' experts, relying extensively on various publications by Kenneth Rothman, an epidemiologist from Boston University who has repeatedly endeavored to challenge the "'conventional wisdom about case-control studies'" – i.e., that they provide less "'valid measures [than those] obtained from cohort studies.'" (*See, e.g.*, Dep. of Christian Merlo, M.D., M.P.H. ("Merlo Dep.") 268:19-269:20, Apr. 18, 2019 (attached as Ex. B9 to Tersigni Cert.).) Of course, Rothman's acknowledgment that he is challenging conventional wisdom confirms that his is an outlier view. In addition, when read in context, Rothman's various papers suggest not that cohort studies are weaker than case-control studies as a general matter, but rather that the general rule might be subject to exceptions, where, for example, a particularly well-designed case-control study is compared to a poorly designed cohort study. (*See id.* 274:14-275:10.) Notably, plaintiffs ignore the fact that when Rothman himself evaluated the relationship between talc and ovarian cancer, he concluded that a causal

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The lowest quality of evidence comes from case reports, case series and other descriptive studies. Case reports are detailed reports of individual outcomes that investigators have found interesting. Although they are helpful tools in generating hypotheses about associations between exposures and outcomes, the lack of a comparison group and other issues limit their ability to establish causal associations between exposure and outcome.[21]

To date, there have been no randomized clinical trials regarding talc use and ovarian cancer, and the parties' experts do not generally rely on case reports.[22] As a result, observational studies addressing this issue, including cohort studies and case-control studies, provide the most relevant epidemiologic data.

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relationship had not been established. *See* Rothman et al., *Interpretation of Epidemiologic Studies on Talc and Ovarian Cancer* at 1 (2000) ("Rothman 2000") (attached as Ex. A126 to Tersigni Cert.) (concluding that "the evidence to date does not indicate that talc can be 'reasonably anticipated to be a human carcinogen'" and that either recall bias or confounding could "readily" or "easily" account for the "overall weak association of a relative risk of 1.31" in case-control studies).

[21] (Merlo Rep. at 9.)

[22] The lack of randomized clinical trials is likely due to the fact that it is considered unethical to test exposures if the hypothesis of the study is that a substance is harmful to human health. (*See, e.g.*, Holcomb Rep. at 8.)

2. Relative Risks And Odds Ratios

Epidemiological studies generally report their results in terms of relative risks ("RR") and odds ratios ("OR") (sometimes additionally referred to as "point estimates" or hazard ratios ("HR")). For purposes of evaluating general causation in this litigation, these are essentially interchangeable concepts that describe the increase (or decrease) in risk between exposure and disease. For example, an odds ratio of 1.0 means that the disease was found to occur no more frequently than in the general (referential) population.[23] An odds ratio of 2.0 means that the disease was found to occur twice as frequently (representing a 100% increased risk), and an odds ratio of 0.5 means the disease was found to occur half as frequently (representing a 50% decrease in risk).

In computing study results, epidemiologists provide a range of values, commonly referred to as a confidence interval, in order to determine whether their findings are statistically significant.[24] A confidence interval provides 95% certainty of the true risk estimate and is intended to ensure that scientists do not advance theories that are based on pure chance.[25] If the confidence interval includes 1.0 (i.e., the possibility of no association), it cannot be said with 95

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23 *See, e.g.*, Epidemiology Reference Manual at 627.

24 (Diette Rep. at 7.)

25 (*Id.*; Holcomb Rep. at 19.)

percent confidence that there is any association between the exposure and the outcome.[26] A related concept is a p-value. A p-value provides a probability that the null hypothesis is true – i.e., that there is no association between exposure and outcome.[27] A p-value less than 0.05 is generally considered to support an association in a study.[28] As discussed below, *see* pp. 63-66, several of plaintiffs' experts support abandoning confidence intervals and p-values – despite the long-established role of these concepts in the scientific community – because doing so would make the case-control studies appear more consistent. This further demonstrates the results-oriented nature of their methodologies.

### B. The Body Of Epidemiologic Literature Related To Talc And Ovarian Cancer

As plaintiffs' own experts concede, ***no cohort study conducted to date shows an overall association between talc use and ovarian cancer –*** and approximately half of the talc case-control studies show a weak, statistically-significant association between the two.[29] In the last 20 years, there have been four

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26 (Diette Rep. at 7.)

27 (*See* Expert Report of Karla Ballman, Ph.D. ("Ballman Rep.") at 17, Feb. 25, 2019 (attached as Ex. C25 to Tersigni Cert.).)

28 (*Id*. at 27.)

29 (*E.g.*, Expert Report of Cheryl Saenz, M.D. ("Saenz Rep.") at 9, Feb. 25, 2019 (attached as Ex. C12 to Tersigni Cert.) (explaining that 54% of the case-control studies have not shown a statistically significant increased risk); Moorman *(cont'd)*

published studies reporting on the results of three large cohort studies examining the putative talc-ovarian cancer association:

- ***Gertig 2000***.[30] This study reported on the Nurses' Health Study ("NHS"), which initially followed 121,700 women for 14 years and later followed 108,870 women for another 10 years. After 14 years, the Gertig paper found no statistically significant association with ovarian cancer for perineal talc use (RR 1.09 (95% CI: 0.86-1.37)), use of talc on sanitary napkins, or for both uses combined, though it reported a weak statistically significant association for HGSOC (RR 1.40 (95% CI: 1.02-1.91)).[31] The Gertig study further showed no statistically significant association for various different frequencies of use and no indication that risk increased with more frequent use. *Id.* The authors concluded that their "results provide ***little support for any substantial association*** between perineal talc use and ovarian cancer risk."[32]

- ***Gates 2010***.[33] This study reported on the NHS after 10 additional years of follow-up. It reported no statistically significant elevation in risk for ***any ovarian subtype***.[34] In other words, "with the passage of an

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Rep. at 18 ("[T]he cohort studies do not show a statistically significant association for ever use of talc and ovarian cancer overall."); Dep. of Ellen Blair Smith, M.D. ("Smith Dep.") 222:10-14, Jan. 9, 2019 (attached as Ex. B11 to Tersigni Cert.) (Q. "None of the cohorts performed today have found an association, correct?" A. "That is true.").)

[30] Gertig et al., *Prospective Study of Talc Use and Ovarian Cancer*, 92 J. Nat. Cancer Inst. 249 (2000) ("Gertig 2000") (attached as Ex. A45 to Tersigni Cert.).

[31] *Id.* at 251.

[32] *Id.* at 252 (emphasis added).

[33] Gates et al., *Risk Factors for Epithelial Ovarian Cancer by Histologic Subtype*, 171(1) Am. J. Epidemiology 45 (2010) ("Gates 2010") (attached as Ex. A42 to Tersigni Cert.).

[34] *Id.* at 45 (RR 1.06 (95% CI: 0.89-1.28) for all subtypes; RR 1.06 (95% CI: 0.84-1.35) for HGSOC).

additional 10 years of time and the diagnosis of an additional 490 cases of ovarian cancer," the slight increase in risk for HGSOC reported in Gertig 2000 had been erased.[35]

- ***Houghton 2014***.[36] This study reported on the Women's Health Initiative ("WHI"), which was one of the largest studies ever conducted on women's health in the United States and followed 61,576 women for an average of 12.4 years.[37] It reported no increased risk of ovarian cancer generally from genital use of talc (HR 1.12 (95% CI: 0.92-1.36)) and no evidence that risk increased the longer women used talc.[38] The authors concluded: "Based on our results, perineal powder use ***does not appear to influence ovarian cancer risk***."[39]

- ***Gonzalez 2016***.[40] This article reported on the Sister Study – a third large cohort study of more than 50,000 women who had sisters who were diagnosed with breast cancer (and were therefore "more likely than the general population to develop ovarian cancer").[41] After 6.5 years of follow-up, it failed to report an association between talc use and ovarian cancer among study subjects (who were 61, on average, at the end of the study).[42] As noted above, the study did report an association between douching and ovarian cancer and further noted that douching and talc use

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35 (Saenz Rep. at 14.)

36 Houghton et al., *Perineal Powder Use and Risk of Ovarian Cancer*, 106(9) J. Nat. Cancer Inst. (2014) ("Houghton 2014") (attached as Ex. A65 to Tersigni Cert.).

37 *Id.* at 1.

38 *Id.* The study reported no increased risk of ovarian cancer from genital talc use for 10 or more years (HR 0.98 (95% CI: 0.75-1.29)) or 20 or more years (HR 1.10 (95% CI: 0.82-1.48)); it further reported no increased risk of ovarian cancer with talc use on sanitary napkins (HR 0.95 (95% CI: 0.76-1.20)) or contraceptive diaphragms (HR 0.92 (95% CI: 0.68-1.23)). *Id.*

39 *Id.* (emphasis added).

40 Gonzalez 2016.

41 *Id.* at 800.

42 *Id.* at 800-02 (HR 0.73 (95% CI: 0.44-1.2)).

> were correlated, suggesting that douching may be a confounding variable in the relevant case-control studies.[43]

In short, the cohort studies have followed more than ***200,000 women*** and collectively reached the same conclusion: ***perineal talc use does not elevate ovarian cancer risk***.[44]

In addition to the cohort studies, there have been approximately 33 case-control studies (26 population-based and seven hospital-based)[45] on talc and ovarian cancer.[46] Approximately half of the case-control studies (and all the hospital-based studies) have not found a statistically significant association

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[43] *Id.* at 800.

[44] Some of plaintiffs' experts have speculated that the lack of a significant overall association between ever use of talc and ovarian cancer in the cohort studies may be due to the fact that they were not adequately powered to detect the weak relative risk identified in certain case-control studies. (*See, e.g.*, Moorman Rep. at 25.) But, as explained below, the peer-reviewed Berge 2018 meta-analysis analyzed this issue and concluded that the cohort studies are adequately powered. *See* Berge 2018 at 253 (the "[l]ow power of cohort studies cannot be invoked as [an] explanation" for the lack of an association reported in the cohort studies).

[45] There are two types of case-control studies at issue here: hospital-based studies, which generally gather "cases" of women who have ovarian cancer and "controls" who are hospitalized for other reasons; and population-based studies, in which the "cases" are women (often from a specified community) who have ovarian cancer and the "controls" are healthy women in the general population, who are typically selected by random telephone dialing.

[46] (*E.g.*, Merlo Rep. at 12.) It is unsurprising that there have been many more case-control than cohort studies because case-control studies can be conducted much more quickly and are far less expensive than cohort studies. *See, e.g.*, Penninkilampi 2018 at 47.

between talc use and ovarian cancer.[47] The remaining case-control studies report relative risks ranging from approximately 1.2 to 1.6.[48] None of these studies has taken the position that its findings, whether by their own force or in combination with other studies, prove a causal relationship between perineal talc use and ovarian cancer. To the contrary, individual studies – ***including studies by plaintiffs' experts*** – have repeatedly expressed that their findings ***do not*** establish causation.[49]

Finally, meta-analyses and pooled studies have generally reported an overall relative risk of approximately 1.3. A meta-analysis is a "type of systematic [literature] review that utilizes a comprehensive, rigorous and standardized approach to selecting, assessing and synthesizing all relevant studies on a given

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47 (*E.g.*, Saenz Rep. at 9; Diette Rep. at 11; Holcomb Rep. at 10 & tbl. 1.)

48 (Holcomb Rep. at 10 & tbl. 1.)

49 *See, e.g.*, Moorman et al., *Ovarian Cancer Risk Factors in African-American and White Women*, 170(5) Am. J. Epidemiology 598, 605 (2009) ("Moorman 2009") (attached as Ex. A95 to Tersigni Cert.) (cautioning that "there is a clear need for additional studies in order to deepen our understanding of causative and protective factors in this population"); *see also, e.g.*, Cramer et al., *Presence of Talc in Pelvic Lymph Nodes of a Woman With Ovarian Cancer and Long-Term Genital Exposure to Cosmetic Talc*, 110 Obstetrics & Gynecology 498, 500 (2007) (attached as Ex. A24 to Tersigni Cert.) (case study co-authored by plaintiffs' experts in state-court talc litigation stating "we are not claiming that a causal relationship between ovarian cancer and talc use is proven for this case or in general").

topic."[50] Epidemiologists use meta-analyses to derive an overall statistical summary of the results of multiple studies that address the same research question.[51] Meta-analyses are particularly useful when individual studies are not conclusive because of small sample size.[52] The term meta-analysis includes both pooled studies (which synthesize the underlying, individual patient data from published studies) and true meta-analyses (which synthesize the summary results of the individual studies and do not incorporate individual patient data).[53] It is well-recognized that the value of both meta-analyses and pooled studies depends on the quality of the underlying studies they examine as well as the soundness of the methods used to select and synthesize the data included.[54] While a well-conducted meta-analysis of randomized clinical trials would in some instances be considered the highest form of causation evidence, a poorly conducted meta-analysis focusing on case-control studies would provide only weak evidence.[55]

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50 (Merlo Rep. at 11.)

51 (*Id.*)

52 (*Id.*)

53 (Ballman Rep. at 2-3.)

54 (*See generally, e.g.*, Holcomb Rep. at 13; Saenz Rep. at 8.)

55 *See, e.g.*, Egger et al., *Rationale, potentials, and promise of systematic reviews, in Systematic Reviews in Health Care: Meta-Analysis in Context* 3, 5 (M. Egger, G.D. Smith, D.G. Altman, eds. 2001) (attached as Ex. A30 to Tersigni Cert.); *id*. at 5 (distinguishing between meta-analyses of randomized trials and

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This is because meta-analyses and pooled studies simply aggregate information from the individual studies on which they report, and therefore are limited by all of the same biases and confounding factors that may skew the results of the underlying studies.[56] *See E.R. Squibb & Sons, Inc. v. Stuart Pharm.*, No. 90-1178 (AET), 1990 U.S. Dist. LEXIS 15788, at *41-42 (D.N.J. Oct. 16, 1990) (acknowledging theoretical utility of meta-analysis but rejecting use of one that included a poor-quality study).

Here, the 1.3 relative risk observed in several meta-analyses stems entirely from the case-control studies. For example, Berge 2018 reported an overall relative risk of 1.22 (95% CI 1.13-1.30), but stratified its results to report relative risks of 1.26 and 1.02 (non-statistically significant) for case-control and cohort studies, respectively.[57] Similarly, Penninkilampi 2018 reported an overall odds ratio of 1.31, but its stratified results showed an odds ratio of 1.35 for case-control

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meta-analyses of observational studies by noting that, due to confounding and bias, "[c]ombining a set of [observational] studies will [] often provide spuriously precise, but biased, estimates of associations").

56 (Saenz Rep. at 16.)

57 Berge 2018 at 251.

studies and a non-statistically significant odds ratio of 1.06 (95% CI 0.90-1.25) for cohort studies.[58]

The meta-analyses and pooled studies have consistently acknowledged that the available evidence does not establish causation. For example, a 2008 meta-analysis co-authored by plaintiffs' expert Dr. Siemiatycki concluded: "The current body of experimental and epidemiological evidence is ***insufficient to establish a causal association*** between perineal use of talc and ovarian cancer risk."[59] The two meta-analyses published last year similarly concluded that "a certain causal link between talc use and ovarian cancer has ***not yet been established***,"[60] and that

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[58] Penninkilampi 2018 at 44. Two of plaintiffs' favored meta-analyses excluded the Gates follow-up from the Nurses' Health Study, but do not indicate why. *See* Penninkilampi 2018 at 46; Taher et al., *Systematic Review and Meta-Analysis of the Association between Perineal Use of Talc and Risk of Ovarian Cancer* (2018) (unpublished manuscript) ("Taher 2018") (attached as Ex. A137 to Tersigni Cert.) at 29 fig. 2 (both excluding Gates). Notably, Dr. Siemiatycki took a different position in his report, excluding Gertig 2000 rather than Gates 2010 from his meta-analysis because the latter "[s]ubsumed" the former. (Siemiatycki Rep. at 95 & tbl. A1.)

[59] Langseth 2008 at 359 (emphasis added); *see also, e.g.*, Terry 2013 at 811 (abstract) ("Whether risk increases with number of genital powder applications and for all histologic types of ovarian cancer also ***remains uncertain*** . . . . Among genital powder users, we observed ***no significant trend in risk with increasing number of lifetime applications***.") (emphases added). The Terry authors also stated that "[t]he main epidemiological evidence against the association is the ***absence of clear exposure-response associations in most studies***, as well as the ***absence of an overall excess risk in the cohort study***." Terry 2013 (emphases added).

[60] Penninkilampi 2018 at 42 (emphasis added).

the available evidence did "***not support a causal interpretation*** of the association."[61]

As detailed below, all observational studies have a number of inherent limitations, including the fact that it is impossible to accurately measure participants' talc exposure. As plaintiffs' experts variously acknowledge, "[m]easuring the 'dose' of talcum powder used by an individual woman is difficult . . . and has been dependent on recall by the woman," with inconsistent "patterns of talc exposure" additionally contributing to "inaccurate estimates of total exposure."[62] Studies therefore cannot determine how much talcum powder

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[61] Berge 2018 at 256 (emphasis added). Plaintiffs' experts have indicated that they will additionally rely on an unpublished 2018 meta-analysis (Taher 2018), which was not peer-reviewed but was nevertheless prominently cited in the "Draft screening assessment" of talc promulgated by Health Canada in December 2018. *See* Draft Screening Assessment. The Taher paper was first "published" on a website sponsored by the Beasley Allen law firm. *See* https://truthabouttalc.com/wp-content/uploads/2018/12/2018-Taher.pdf. As set forth below, the Taher meta-analysis and Draft Screening Assessment report odds ratios similar to the other 2018 meta-analyses and likewise fail to conclude that the evidence establishes causation.

[62] (*See, e.g.*, Clarke-Pearson Rep. at 9; Moorman Rep. at 30; *see also*, *e.g.*, McTiernan Rep. at 23; Singh Rep. at 64; Expert Report of Judith Wolf, M.D. ("Wolf Rep.") at 15, Nov. 16, 2018 (attached as Ex. C23 to Tersigni Cert.) (all similar).) As a 2015 review of the talc literature further explained, studies have also failed to "characterize[] . . . the feminine hygiene habits involving the use of cosmetic talc products," in part because the studies have not used specific enough questionnaires, potentially confusing participants as to "the distinction between talc or talcum powders and talc-free powders when answering the questions." Fiume et al., *Safety Assessment of Talc as Used in Cosmetics*, 34(1 Suppl.) Int'l J

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reportedly used by participants was actually applied to the perineum, let alone how much, if any, "actually reache[d] the [fallopian] tubes and ovaries" (where pre-cancerous biological effects are alleged to take place).[63]

Further, a number of studies have noted that the weak association reported in many of the case-control studies (but no cohort studies) could be explained entirely by limitations inherent in the case-control study design, including recall bias and confounding factors. As one recent study explained, recall bias (i.e., cases and controls remembering past exposures differently, even if the usage rate between the groups is the same) is especially problematic when studying talc use because it is exceedingly difficult for study subjects to accurately report the extent of their use, which "require[s] subjective summarization or can be influenced by the investigator, media or similar factors."[64] Similarly, the 2018 Berge meta-analysis

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Toxicol. 66S, 117S (2015) ("Fiume 2015") (attached as Ex. A37 to Tersigni Cert.). According to Fiume, "[t]hese factors contribute substantially to the uncertainties associated with the risk estimates" from the relevant studies. *Id.* In short, across the many studies that have evaluated perineal talc use, there is no uniformity concerning the products used, the amount that constitutes a "dose" of the products, or the means of application of those products (i.e., whether applied by sprinkling on the perineum or to sanitary pads or underwear, for example).

63 (Wolf Rep. at 15; Smith Rep. at 20 (similar).)

64 Peres et al., *Racial/ethnic differences in the epidemiology of ovarian cancer: a pooled analysis of 12 case-control studies*, Int'l J Epidemiol. 1, 10 (2017) ("Peres 2017") (attached as Ex. A111 to Tersigni Cert.).

noted that "[t]he fact that the association between genital talc use and risk of ovarian cancer is present in case-control, but not in cohort studies, ***can be attributed to bias in the former type of studies***."[65] And the 2008 meta-analysis co-authored by plaintiffs' expert Dr. Siemiatycki noted that "women with the cancer tend to remember or overreport their use of body powder" and that the "***influence of this type of recall bias cannot be ruled out***."[66]

The recall-bias problem associated with case-control studies has been exacerbated by media coverage of talcum powder litigation. A 2016 study co-

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[65] Berge 2018 at 253 (emphasis added).

[66] Langseth 2008 at 358 (emphasis added). The studies plaintiffs' experts rely on resoundingly acknowledge this concept. Terry 2013 at 820 ("These [case-control] studies were retrospective in nature and therefore potentially susceptible to bias if cases were more likely to report genital powder use than controls."); Taher 2018 at 42 ("Potentially important sources of bias reported in the included studies include . . . exposure misclassification due to recall bias inherent in case control studies."); Cramer et al., *Genital Talc Exposure and Risk of Ovarian Cancer*, 81 Int'l J. Cancer 351, 354 (1999) ("Cramer 1999") (attached as Ex. A23 to Tersigni Cert.) (noting that "[r]ecall bias is possible because talc exposure in these studies is based on personal recollection") (emphasis added); *see also, e.g.*, Ness et al., *Factors Related to Inflammation of the Ovarian Epithelium and Risk of Ovarian Cancer*, 11(2) Epidemiology 111, 116 (2000) ("Ness 2000") (attached as Ex. A106 to Tersigni Cert.) ("Another limitation of our study is the potential for recall bias, which is a concern with any case-control study."); Cook et al., *Perineal Powder Exposure and the Risk of Ovarian Cancer*, 145(5) Am. J. Epidemiology 459, 459 (1997) ("Cook 1997") (attached as Ex. A21 to Tersigni Cert.) ("Limitations of the present study include . . . the potential differential recall of powder usage."); *see also* IARC 2010 Monograph at 31 (evaluating talc studies and concluding that "chance, bias or confounding could not be ruled out with reasonable confidence" as the cause of the observed association).

authored by plaintiffs' expert Dr. Moorman and others sought to evaluate "the possibility of differential misclassification" (in other words, recall bias) "due to the heightened awareness of" talc-ovarian cancer litigation that resulted from media reports in 2014.[67] The study found that women with ovarian cancer who were interviewed for the study after 2014 reported markedly higher talc use than those interviewed before 2014 (51.5% versus 36.5%), while reported talc use for controls was essentially the same regardless of when they were interviewed.[68] Of particular note, the study found no statistically significant association between talc use and ovarian cancer in the women who were interviewed ***before*** 2014.[69]

Confounding (i.e., study participants having risk factors for ovarian cancer unrelated to talc) is also a potential explanation for the weak association between talc use and ovarian cancer in some case-control studies. For example, one study

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67 Schildkraut 2016 at 1416.

68 *Id.*

69 *Id.* (post-2014 OR 2.91 (95% CI 1.70-4.97); pre-2014 OR 1.19 (95% CI 0.87-1.63)). (*See also* Saenz Rep. at 13 (explaining that recall bias "result[ed] in the inflation of the odds ratio from a non-statistically significant value to a statistically significant one almost 2.5 times higher").) While the Schildkraut study demonstrates the heightened recall bias stemming from recent media coverage of talc lawsuits, its findings do not mean that pre-2014 studies were not susceptible to recall bias. As Dr. Diette explains in his report, there was substantial publicity about the alleged risks of perineal talc use prior to 2014 as well. (Diette Rep. at 19-20; Merlo Rep. at 39.) And recall bias is not limited to situations with substantial publicity – rather, it is an inherent limitation of all case-control studies that are based on personal recollection.

observed that talc users are more likely than nonusers to have a number of risk-increasing characteristics, such as a high BMI,[70] but many studies did not control for these characteristics. And a recent cohort study found that talc users were more likely to douche and that douching ***doubled*** the risk of ovarian cancer,[71] but the vast majority of case-control studies did not adjust for douching.[72]

### C. The Unreliable Methods Employed By Plaintiffs' Experts

Plaintiffs' experts purport to apply the nine Bradford Hill considerations,[73] which are "metrics that epidemiologists use to distinguish a causal connection from a mere association." *In re Zoloft (Sertraline Hydrochloride) Prods. Liab. Litig.*, 858 F.3d 787, 795 (3d Cir. 2017) ("*Zoloft III*"). As Hill explained in a 1965 speech, the nine considerations come into play when "observations reveal an association between two variables, ***perfectly clear-cut and beyond what we would***

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70 Houghton 2014 at 3.

71 Gonzalez 2016 at 799, 800-02.

72 (Merlo Rep. at 33 ("As previous studies (except for Harlow et al. (1992)) did not account for douching, the relatively weak statistically significant associations could potentially be explained by confounding.").) In addition, as Dr. Holcomb explains, previously unknown confounders have been discovered late in the study of diseases and subsequently been confirmed to be true causes. (Holcomb Rep. at 12 (explaining that Herpes Simplex Virus was once thought to cause cervical cancer before improved detection techniques demonstrated that Human Papilloma Virus is instead the cause).)

73 *See generally* Hill, *The Environment and Disease: Association or Causation?*, 58(5) Proc. Royal Soc'y Med. 295 (1965) ("Hill 1965") (attached as Ex. A63 to Tersigni Cert.).

***care to attribute to the play of chance***."[74] Once such a "clear-cut" association has been established, these considerations can guide a determination of whether "the most likely interpretation of [such an association] is causation."[75] The nine considerations enumerated by Hill are: (1) ***strength of association*** (the magnitude of the reported association); (2) ***consistency of association*** (whether different studies consistently report the association); (3) ***specificity*** (whether the variable is associated with a specific disease); (4) ***temporality*** (whether the exposure precedes disease onset); (5) ***coherence*** (whether the causal hypothesis is logical or contradicts existing knowledge); (6) ***dose response*** or ***biological gradient*** (whether greater exposure increases risk or vice versa); (7) ***biological plausibility*** (whether there is a valid means through which an agent could cause the disease); (8) ***experimental evidence*** (whether experimental studies support the posited association); and (9) ***analogy*** (whether the association can reasonably be compared to other associations that have been accepted as causal).[76]

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74 Hill 1965 at 295 (emphasis added).

75 *Id.*

76 *Id*. at 295-99.

Plaintiffs' experts generally opine that each of these considerations weighs in favor of causation or is neutral/irrelevant,[77] but a review of their opinions against the backdrop of the relevant studies and regulatory pronouncements makes clear that their analyses are not grounded in science or the scientific method.

## ARGUMENT

Rule 702 provides that expert testimony is admissible only if the witness is qualified and the opinion is "based on sufficient facts or data" and "the product of reliable principles and methods" that have been "reliably applied . . . to the facts of the case." Fed. R. Evid. 702.[78]

To determine whether expert testimony is reliable, a court must assess "whether the reasoning or methodology underlying the testimony is scientifically valid and . . . whether that reasoning or methodology properly can be applied to the

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[77] (Carson Rep. at 8-11; Clarke-Pearson Rep. at 8-9; Expert Report of Sarah Kane, M.D. ("Kane Rep.") at 33-37, Nov. 15, 2018 (attached as Ex. C38 to Tersigni Cert.); McTiernan Rep. at 63-68; Moorman Rep. at 10-40; Siemiatycki Rep. at 61-67; Singh Rep. at 62-66; Smith-Bindman Rep. at 35-41; Smith Rep. at 19-21; Wolf Rep. at 13-16.)

[78] An expert must qualify as an expert under Rule 702 "by knowledge, skill, experience, training, or education." Fed. R. Evid. 702. Additionally, an expert's opinion is only admissible if it "help[s] the trier of fact to understand the evidence or to determine a fact in issue." *Id.* As the Supreme Court explained in *Daubert*, this "'helpfulness' standard requires a valid scientific connection to the pertinent injury as a precondition to admissibility." *Daubert v. Merrell Dow Pharm., Inc.*, 509 U.S. 579, 591-92 (1993). "The consideration has been aptly described . . . as one of 'fit,'" which "goes primarily to relevance." *Id.* at 591 (citation omitted).

facts in issue." *Daubert*, 509 U.S. at 600 (citation omitted). "[C]ourts can consider multiple factors, including the testability of the hypothesis, whether it has been peer reviewed or published, the error rate, whether standards controlling the technique's operation exist, and whether the methodology is generally accepted." *Zoloft III*, 858 F.3d at 792. "Both an expert's methodology and the application of that methodology must be reviewed for reliability"; in other words, "the 'techniques' used to implement the [expert's] analysis must be 1) reliable and 2) reliably applied." *Id*. at 792, 796.

As the Third Circuit has stressed, "***any*** step that renders the analysis unreliable under the *Daubert* factors renders the expert's testimony inadmissible." *Id.* at 797 (citation omitted); *see also, e.g.*, *Perry v. Novartis Pharm. Corp.*, 564 F. Supp. 2d 452, 459 (E.D. Pa. 2008) (explaining that this principle holds regardless of "whether the step completely changes a reliable methodology or merely misapplies that methodology") (citation omitted). Moreover, for multi-factorial methodologies such as analyzing the Bradford Hill considerations, "all of the relevant evidence must be gathered, and the assessment or weighing of that evidence must not be arbitrary, but must itself be based on methods of science." *Zoloft III*, 858 F.3d at 796 (citation omitted). Such analyses should be excluded if they are "mere conclusion-oriented selection process[es]." *Id*. (citation omitted). As a different court put it, experts may not advance "unscientific 'black box'

approach[es] to Bradford Hill." *In re Mirena IUS Levonorgestrel-Related Prods. Liab. Litig. (No. II)*, 341 F. Supp. 3d 213, 248-49 (S.D.N.Y. 2018).

Consistent with these principles, courts have repeatedly excluded the opinions of experts who apply the Bradford Hill factors in name only to reach conclusions that the underlying science does not support. *See, e.g.*, *Zoloft III*, 858 F.3d at 798-800 (affirming exclusion of expert whose Bradford Hill analysis relied on, *inter alia*, a "conclusion-driven" re-analysis of past studies, unreliable "ad hoc adjustments" to epidemiological data and an inconsistent consideration of statistically insignificant study results); *Soldo v. Sandoz Pharm. Corp.*, 244 F. Supp. 2d 434, 514 (W.D. Pa. 2003) (excluding expert witnesses whose "efforts to apply the Bradford Hill considerations to the available evidence" were "not scientifically reliable" and granting summary judgment for the defendant); *Magistrini v. One Hour Martinizing Dry Cleaning*, 180 F. Supp. 2d 584, 604 (D.N.J. 2002) (excluding Bradford Hill-based causation opinion where the expert "did not adequately explain his methods for assessing the[ir] internal validity"), *aff'd*, 68 F. App'x 356 (3d Cir. 2003).[79]

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[79] *See also, e.g.*, *Dunn v. Sandoz Pharm. Corp.*, 275 F. Supp. 2d 672, 679 (M.D.N.C. 2003) (excluding expert whose "application of the Bradford Hill criteria does not satisfy the reliability prong of *Daubert*"); *Caraker v. Sandoz Pharm. Corp.*, 172 F. Supp. 2d 1046, 1049 n.5 (S.D. Ill. 2001) (excluding causation expert whose Bradford Hill analysis consisted largely of "curt

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As set forth below, plaintiffs' experts' general causation opinions are inadmissible under these standards because they have engaged in the exact sort of unscientific, results-oriented analysis that the Third Circuit and other courts have deemed unreliable. In addition, Dr. Smith-Bindman's meta-analysis was unreliable because she undertook a "post hoc" analysis after reviewing the data and used inconsistent inclusion and exclusion criteria. Finally, Drs. Moorman and Siemiatycki's litigation opinions are separately invalid because they contradict these experts' pre-litigation published writings.

## I. PLAINTIFFS' EXPERTS ARRIVED AT THEIR CAUSATION OPINIONS THROUGH UNRELIABLE AND CONCLUSION-DRIVEN BRADFORD HILL ANALYSES.

### A. Plaintiffs' Experts' Conclusion That A Facially Weak Association Is A Strong One Is Patently Unreliable.

#### 1. The Only Possible Conclusion From The Relevant Data Is That Any Association Is Weak.

"[S]trength of association" is "first upon [the] list" of factors to be considered in determining whether an association between two variables is causal.[80] The epidemiological studies addressing the posited link between talc and ovarian cancer collectively show, at most, an approximately 1.2-1.6 relative risk

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conclusions making vast assumptions" and whose analysis appeared to be an "afterthought" designed to justify the expert's conclusions).

[80] Hill 1965 at 295.

between perineal talc use and ovarian cancer.[81] As courts have recognized, this is a weak, not strong, association by any objective measure. *See Carl*, 2016 WL 4580145, at *18 (observing that the talc studies showed a "uniformly weak . . . association").[82] Further, such an association is a far cry from the examples of a ***200% to 1000%*** increase in risk that Hill originally identified as supportive of causation.[83]

While a number of plaintiffs' experts assert in their reports that a "significant" or "strong" association has been reported between talc use and ovarian cancer,[84] many were forced to concede at their depositions that this is not

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[81] While several of plaintiffs' experts identify a relative risk of 1.5 or 1.6 (*see* Singh Rep. at 17, 63 (reporting a 30% to 60% increased risk); Smith Rep. at 16 (reporting an "increased risk [of] "approximately 20-50%")), the meta-analyses on which plaintiffs' experts rely report a relative risk ranging from 1.2 to 1.3, *e.g.*, Berge 2018 at 248; Penninkilampi 2018 at 41.

[82] These risk ratios also fall well short of the 2.0 figure courts often require as a lower threshold for proving that a variable more likely than not caused a disease. *See, e.g.*, *Magistrini*, 180 F. Supp. 2d at 591 ("[T]he threshold for concluding that an agent was *more likely than not* the cause of an individual's disease is a relative risk greater than 2.0.") (citation omitted).

[83] Hill 1965 at 297. (*See also* Holcomb Rep. at 19-20 (smoking is associated with a 10- to 30-fold increased risk of lung cancer and HPV is associated with a 50- to 100-fold increased risk of cervical cancer (compared to the, at most, 1.6-fold increase reported for talc)); Bosch et al., *The causal relation between human papillomavirus and cervical cancer*, 55(4) J. Clin. Pathol. 244 (2002) (attached as Ex. A13 to Tersigni Cert.) (reporting an odds ratio of ***83.3*** for HPB and cervical cancer).

[84] (*See* Singh Rep. at 17 (asserting that the "strength of association . . . is

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the case – and that a risk ratio in the range of 1.2-1.6 is instead only a "weak" or, at best, "modest" association.[85] Others in the scientific community have similarly characterized relative risks in this range as "weak" or "small," i.e., not strong.[86]

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significant"); Smith-Bindman Rep. at 37 (noting an "extremely strong" association); Smith Rep. at 19 (noting a "significant" association); Carson Rep. at 9-10 ("strong" and "compelling strength of association" assigned the "most weight" in opining that talcum powder causes ovarian cancer); McTiernan Rep. at 63-64 (increased risk of 22-31% "strongly supports a causal association" and given "high weight" for causality opinion); Siemiatycki Rep. at 62-63 (asserting that "the meta-[risk ratio] of 1.28" is "high and significant"); Singh Rep. at 63 ("I place significant weight on the fact that studies demonstrate a strong association between talcum powder use and ovarian cancer . . . ").)

[85] (*E.g.*, Dep. of Arch I. Carson, M.D., Ph.D. ("Carson Dep.") 230:18-231:5, 232:13-233:23, Jan. 19, 2019 (attached as Ex. B5 to Tersigni Cert.) ("weak or modest"); Dep. of Sarah E. Kane, M.D. ("Kane Dep.") 256:24-257:4 (attached as Ex. B45 to Tersigni Cert.) (similar); Dep. of Sonal Singh, M.D., M.P.H. ("Singh Dep.") 140:19-25, Jan. 16, 2019 (attached as Ex. B47 to Tersigni Cert.) (similar).) Correspondingly, plaintiffs' experts have been unable to identify any scientific source characterizing a relative risk in the 1.2-1.6 range as probative of a strong association. (*E.g.*, Dep. of Daniel L. Clarke-Pearson, M.D. ("Clarke-Pearson Dep.") 130:10-15, Nov. 16, 2018 (attached as Ex. B10 to Tersigni Cert.) (failing to identify any peer-reviewed literature on talc and ovarian cancer that states 1.3 is a strong association); Moorman Dep. 251:9-13 (same); Singh Dep. 140:19-141:20 (same); Smith Dep. 289:19-290:3 (same).)

[86] Wynder et al., *Weak Associations in Epidemiology and Their Interpretation*, 11 Preventive Med. 464, 465 (1982) ("Wynder 1982") (attached as Ex. A157 to Tersigni Cert.) ("the term 'weak' refers to relative risks between 1.0 and 2.0"); Draft Screening Assessment at 21 ("small" association); FDA Denial Letter at 4 ("small positive associations"); Berge 2018 at 248 ("weak" association). (*See also* Dep. of Anne McTiernan, M.D., Ph.D. ("McTiernan Dep.") 101:5-17, Jan. 28, 2019 (attached as Ex. B2 to Tersigni Cert.) (testifying that the World Cancer Research Fund concluded that "[e]ven if there were an increased risk, scientists

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The mere fact that plaintiffs' experts opine that strength of association supports a causal conclusion based on an objectively weak magnitude of risk itself highlights the unreliability of their methodologies. *See, e.g.*, *Soldo*, 244 F. Supp. 2d at 515 (excluding experts who did not establish an association between the drug Parlodel and stroke, "much less a strong association," and did not "cite[] reliable scientific evidence establishing such an association"); *In re Zoloft (Sertraline Hydrochloride) Prods. Liab. Litig.*, 26 F. Supp. 3d 449, 463 (E.D. Pa. 2014) ("*Zoloft I*") (excluding general causation opinion where, *inter alia*, "the strength of the associations between exposure to Zoloft and the various birth defects at issue [wa]s weak, often not greater than one would expect by chance alone").

And it is especially unreliable for plaintiffs' experts to characterize the objectively "weak" 1.2-1.6 figure as indicative of a strong association because that figure itself is artificially inflated by the fact that it is based primarily on case-control studies.[87] As set forth above, because case-control studies are retrospective in nature, and rely on subjects' recall of the extent or nature of their exposure, they are more likely than cohort studies to report a false association as a result of bias,

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estimate it would be small").)

87 *See* Berge 2018 at 253 ("the association between genital talc use and risk of ovarian cancer is present in case-control, but not in cohort studies").

confounding or small study size.[88] Indeed, scientists have expressly cautioned that low relative risks observed in case-control studies – including the relative risk range of 1.2-1.6 observed with respect to talc and ovarian cancer – could be ***entirely attributable*** to bias, confounding or chance.[89] For this reason, scientists and courts recognize that weak associations do not support causation, and other convincing scientific evidence is needed to ***overcome*** the absence of a strong association.[90]

As explained above, there is significant evidence that the weak association reported in a subset of the case-control studies is ***in fact*** attributable to recall bias

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88 (*See, e.g.*, Diette Rep. at 5, 19; Merlo Rep. at 10, 27.)

89 Wynder 1982 at 471; Epidemiology Reference Manual at 602; Rothman 2000 at 4 ("Recall bias can ***readily introduce enough bias*** to produce the modestly-sized overall effect (RR = 1.3) that emerges from these [talc] studies.") (emphasis added). (*See also* Moorman Dep. 251:2-7 (conceding that "with a smaller association, there is more concern that it could be due to bias"); Dep. of Patricia Moorman, Ph.D., M.S.P.H. ("Moorman *Ingham* Dep.") 59:16-60:3, *Ingham v. Johnson & Johnson*, No. 1522-CC10417-01 (Mo. Cir. Ct. Mar. 12, 2018) (attached as Ex. E2 to Tersigni Cert.) (conceding that "potential bias" "can lead to making an inaccurate conclusion . . . either the overall conclusion or the – the strength of the association that you're looking at").)

90 *See, e.g.*, Wynder 1982 at 465 ("the need to seek supporting evidence is greater with weak than with strong associations"); Epidemiology Reference Manual at 602 (explaining that "epidemiologist[s] will scrutinize [weak] associations more closely"); *Zoloft I*, 26 F. Supp. 3d at 456 ("[A]n equally plausible conclusion from multiple studies finding only weak associations, not greater than one would expect by chance, is that the true association is weak; so weak that one cannot conclude that the risk is greater than that seen in the general population.").

and confounding. As noted above, the Schildkraut study found that women interviewed after 2014 (when talc lawsuits began receiving more significant media attention) reported a 15% higher rate of talc use, resulting in a relative risk ***2.5 times higher*** than the non-statistically significant relative risk reported for women interviewed before 2014.[91] Although some of plaintiffs' experts assert that Schildkraut shows that studies published before 2014 are not susceptible to recall bias,[92] these assertions are pure *ipse dixit*. None of plaintiffs' experts has analyzed the historical record to confirm their unsupported supposition that participants in pre-2014 studies were not aware of the allegations linking talc use to ovarian cancer. *See Soldo*, 244 F. Supp. 2d at 563 (refusing to admit "opinion evidence that is connected to existing data only by the *ipse dixit* of the expert" because a court "is not required to simply take the expert's word for it"). By contrast, defendants' expert Dr. Diette notes in his report that there ***was*** in fact media

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91 Schildkraut 2016 at 1414 tbl. 2 (reporting, for post-2014 and pre-2014 interviewees, respectively, 51.5% versus 36.5% talc use and relative risks of 2.91 (95% CI 1.70-4.97) versus 1.19 (95% CI 0.87-1.63)). (*See also* Saenz Rep. at 13 (explaining these findings); Clarke-Pearson Dep. 164:2-11 (conceding that Schildkraut 2016 demonstrated the effect of recall bias); Singh Dep. 261:7- 267:19 (similar).)

92 (*E.g.*, Siemiatycki Rep. at 55; McTiernan Rep. at 24.)

publicity about this issue long before 2014, including in major U.S. newspapers such as the *Chicago Tribune*, *Washington Post* and *San Francisco Chronicle*.[93]

In any event, media attention "is just one element of recall bias," as Dr. Singh conceded.[94] Other causes – including the propensity of "cases" to search their memories for behaviors that they think could have caused their disease and the general difficulty of accurately recalling historical details – exist independently of media coverage and lawsuits.[95] This is particularly so because many talc studies did not blind the participants to the purpose of the study, potentially alerting them that talc use was of interest, even if they had not previously heard about it in the news.[96]

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93 (Diette Rep. at 19-20; Merlo Rep. at 39.)

94 (Singh Dep. 267:5-16.)

95 (*See, e.g.*, Saenz Rep. at 12 (explaining how non-media-driven recall bias operates); Moorman Rep. at 21 (recall bias is possible in case-control studies because "people affected with a disease may have given more thought to possible causes of that disease and have more accurate recall of risk factors than a person serving as a control in the study").) *See also* Peres 2017 at 10 (study co-authored by Dr. Moorman explaining that "self-reported data" inherently presents the "concern" of "recall bias," "especially for characteristics" such as talc use "that are difficult to report with accuracy [and] require subjective summarization").

96 (Ballman Rep. at 7; Moorman Rep. at 21-22 ("recall bias would be considered a particular threat to a study's validity" where, *inter alia*, "the study hypotheses are known to the study subjects or interviewers"); Singh Rep. at 11 "Case-control studies, by their design, are generally not blinded and are also susceptible to bias as a result.").)

In addition, although plaintiffs' own expert, Patricia Moorman, has noted that "[i]f you do not control for confounding" factors in a study, "it is a potential bias" that can "lead to making an inaccurate conclusion" about causation,[97] plaintiffs' experts generally ignore several confounding factors that have been tied to talc use and ovarian cancer. Most notably, the 2016 Gonzalez study suggests that douching – ***not talc use*** **–** might account for the association observed in case-control studies. Specifically, that study found that talc users are more likely to douche than the general population,[98] and that douching nearly doubled the risk of ovarian cancer.[99] This is a significant finding because only a couple of case-control studies have adjusted for douching.[100]

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97 (Moorman *Ingham* Dep. 59:16-60:3.)

98 Gonzalez 2016 at 800 (concluding that douching and talc use "are correlated"); *id.* at 797 ("Behavioral correlation between talc use and douching could produce confounding."); *see also* Rosenblatt et al., *Characteristics of Women Who Use Perineal Powders*, 92(5) Obstetrics & Gynecology 753, 754 (1998) ("Rosenblatt 1998") (attached as Ex. A124 to Tersigni Cert.) ("A relatively higher proportion of women who used [talcum] powder . . . also had douched . . ., consumed alcohol . . ., or smoked cigarettes. Women in the highest BMI were relatively more likely ever to have used powder in the perineal area"); Houghton 2014 at 3 (similarly observing that talc users are more likely than nonusers to have a number of risk-increasing characteristics).

99 Gonzalez 2016 at 801 ("Ever douching during 12 months prior to study entry was associated with increased ovarian cancer risk (adjusted HR: 1.8, 95% CI: 1.2, 2.8; Table 2).").

100 Gonzalez 2016 at 797. (*See* Merlo Rep. at 33 (explaining that only Gonzalez 2016 and a 1992 case-control study accounted for douching); Siemiatycki Rep. at

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And douching is only one example of this problem. As Dr. Merlo notes, the case-control studies failed to consistently adjust for various potential confounding factors, with some studies failing to consider confounders at all and others accounting for only some of the factors that might explain an association with ovarian cancer, e.g., family history of cancer, menopausal status, BMI and contraceptive use.[101] Dr. Smith-Bindman acknowledges this point, conceding that talc case-control studies have not uniformly assessed and controlled for confounders.[102]

Adjustment for confounding is particularly important because, in addition to numerous established risk factors for ovarian cancer, most cases of ovarian cancer

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100-102 (table identifying covariates analyzed in the talc literature showing douching only considered in one study).) A small hospital-based study by Hartge discussed in note 105, *infra*, considered douching as well, but that study had a very small sample size and, in any event, found no association between talc use and ovarian cancer either.

[101] (*See* Merlo Rep. at 13.)

[102] (Dep. of Rebecca Smith-Bindman, M.D., Vol. II ("Smith-Bindman 2/8/19 Dep.") 307:21-308:24, Feb. 8, 2019 (attached as Ex. B42 to Tersigni Cert.) (talc studies "didn't all adjust for the same covariates").) The failure to adjust for confounders in a uniform manner is particularly problematic for meta-analyses because, as noted above, compiling the studies does not eliminate the various confounding issues in the underlying studies (*e.g.*, Moorman Dep. 159:11-14); to the contrary, merging inconsistent confounding data can exacerbate the problem and generate misleading results (Saenz Rep. at 16; Diette Rep. at 21; Merlo Rep. at 8).

have no known cause, and previously undiscovered risk factors can account for positive associations in observational studies.[103] Nevertheless, the majority of plaintiffs' experts fail to meaningfully address whether the small association reported in case-control studies could be explained by confounding.[104] And only Dr. Moorman addresses douching as a potential confounder (and then rejects it without a reliable basis for doing so).[105] Plaintiffs' experts have thus failed to

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[103] (*See, e.g.*, Dep. of Jack Siemiatycki, Ph.D. ("Siemiatycki Dep.") 173:6-9, Jan. 31, 2019 (attached as Ex. B29 to Tersigni Cert.) (agreeing that "all of the factors that might make someone susceptible to developing ovarian cancer are not currently known"); Saenz Rep. at 4-6 (identifying established and histology-specific risk factors for ovarian cancer); Holcomb Rep. at 12 (explaining that unknown factors can account for associations previously attributed to different factors); Diette Rep. at 4 ("confounding factors are not always identifiable, even after extended study, and these and other factors can consistently drive statistical associations that are not causal in nature").) For example, as Dr. Neel explains, numerous genes increasing the risk of ovarian cancer have been identified since the publication of most talc epidemiological studies, and were accordingly not accounted for in those studies. (Expert Report of Benjamin Neel, M.D., Ph.D. ("Neel Rep.") at 27, Feb. 25, 2019 (attached as Ex. C10 to Tersigni Cert.).)

[104] (*See, e.g.*, Clarke-Pearson Rep. (not discussing confounding); Carson Rep. at 8; Smith Rep. at 16; Wolf Rep. at 8 (all dismissing confounding in single conclusory sentences); *see also, e.g.*, McTiernan Rep. at 24 (opining that confounding is not a problem only because "the studies reviewed performed adjustment for several potential confounding variables").)

[105] (Moorman Rep. at 28.) Dr. Moorman opines, among other things, that the Gonzalez study "showed that adjusting for douching using statistical modelling had a negligible effect on the association between talc use and ovarian cancer" (*id.*), but this assertion is contradicted by the authors' statement that "[i]f douching is a risk factor for ovarian cancer, some of the earlier reports on talc ***could have been subject to confounding bias***," Gonzalez 2016 at 800 (emphasis added). Moorman additionally argues that Harlow 1992 still showed an association for talc use when

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"adequately account[] for obvious alternative explanations." *Mirena*, 341 F. Supp. 3d at 262 (citation omitted) (criticizing Dr. Plunkett for making "no . . . effort" to address confounding factors); *Zoloft I*, 26 F. Supp. 3d at 464 (excluding expert who "d[id] not address" "significant issues with regard to . . . confounding factors" raised by a study; "[the expert] must also consider alternative explanations for the associations seen in the studies she relies upon, especially in light of the lack of consistency and replication").

2. Plaintiffs' Experts Tacitly Admit That The "Strength" Criterion Is Not Satisfied By Improperly Attempting To Redefine The Word Strength As Something Else.

Several of plaintiffs' experts also engage in an unreliable effort to redefine "strength," an effort that only serves to underscore the methodologically flawed nature of their conclusions.

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controlling for douching, but the results of that small study (146 combined cases and controls) say nothing about the unaccounted-for effect of douching in the remainder of the talc literature. *See* Harlow et al., *Perineal Exposure to Talc and Ovarian Cancer*, 80(1) Obstet Gynecol. 19, 22 (1992) ("Harlow 1992") (attached as Ex. A55 to Tersigni Cert.). She further argues that a different, older case-control study (Hartge 1983) reported no association between douching and ovarian cancer, but ignores that the Hartge study also reported "no overall association between ***talc use*** and ovarian cancer." Hartge et al., *Talc and Ovarian Cancer*, 250(14) J. Am. Med. Assoc., 1844, 1844 (1983) (attached as Ex. A56 to Tersigni Cert.) (emphasis added).

***Public Policy Arguments.*** Several of plaintiffs' experts take the position that a 1.2-1.6 relative risk, although mathematically weak, nevertheless should be deemed significant as a matter of policy because it can have a "great[] impact on a number of people" considering the number of women who use talc and the grim prognosis for many ovarian cancers.[106]

This is a litigation argument, rather than a scientific assessment. As Dr. Ballman explains in her report, "[d]etermining the strength of the relationship between an exposure and a disease is not made on the basis of the potential public health impact."[107] After all, the question in a Bradford Hill analysis is whether an exposure causes a disease – not the gravity of the disease at issue.

For similar reasons, courts have repeatedly recognized that precautionary approaches to public health (which might take account of the seriousness of a disease in deciding whether to suggest limiting exposure) are of little relevance to proving causation in litigation. *See, e.g.*, *Tamraz v. Lincoln Elec. Co.*, 620 F.3d 665, 673 (6th Cir. 2010) (explaining that "low threshold" and "precautionary

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106 (Smith-Bindman Rep. at 36-38 (further concluding that strength of association is "important and met" because of the "very large number of cancers to be caused by a product that provides no medical benefit"); *see also, e.g.*, McTiernan Rep. at 64 ("plac[ing] high weight on" strength of association "given the high prevalence of use of talcum powder products in this population," creating a "significant public health concern"); Moorman Rep. at 14; Smith Rep. at 19; Clarke-Pearson Rep. at 8 (all similar).)

107 (Ballman Rep. at 24.)

principle" may "serve[] well in the clinic" – where advising a patient to avoid an exposure "can do little harm, and might do a lot of good" – but it does "not in the courtroom, where decision requires not just an educated hunch but at least a preponderance of the evidence"); *McClain v. Metabolife Int'l, Inc.*, 401 F.3d 1233, 1249 (11th Cir. 2005) (explaining that "the type of risk assessment that a government agency follows for establishing public health guidelines" differs from "an expert analysis of toxicity and causation in a toxic tort case"). In short, a plaintiff's causation burden cannot be diminished simply because the alleged disease is severe.

***Emphasis On Causal Relationships With Weak Associations.*** Plaintiffs' experts additionally attempt to cast a 1.2-1.6 association as "strong" by comparing it to other exposures that have been deemed to cause disease despite low relative risks, such as second-hand smoking and lung cancer, or hormone therapy and breast cancer.[108] But the fact that some low elevations in risk have been regarded

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[108] (*E.g.*, Moorman Rep. at 12-13 (discussing "some other well-accepted exposure-disease associations that have relative risks of similar magnitude and are generally accepted to be causal"); Moorman Dep. 245:10-16 (testifying that the association is "strong enough" because there are "numerous examples of well-accepted causal associations that are of a similar magnitude"); Siemiatycki Rep. at 62, 87-88 tbl. 11 (identifying other exposures that he opines have similar risk ratios and are "well-recognized risk factors for cancer and other diseases"); Singh Rep. at 63 ("There are several noteworthy examples of well-established causal

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as causal in other circumstances where other Bradford Hill factors – such as dose-response, consistency and biological plausibility – were particularly compelling does not mean that all low observed associations may be considered causal. To the contrary, it is a fundamental principle of epidemiology (and a premise of the Bradford Hill criteria) that "lower relative risks" must be "scrutinize[d] . . . more closely." *See, e.g.*, Epidemiology Reference Manual at 602; *cf. Magistrini*, 180 F. Supp. 2d at 606 ("[A] relative risk of 2.0 is not so much a password to a finding of causation as one piece of evidence . . . .").

Here, because none of plaintiffs' experts has conducted a systematic review of the literature with respect to second-hand smoke or hormone therapy, they are in no position to say that the evidence supporting causal associations for those exposures is of similar quality to the data on talc use. The expert who comes closest is Dr. Moorman, who provides a single paragraph summarizing the findings of one meta-analysis of studies on second-hand smoking and lung cancer.[109] But Dr. Moorman conceded that she did not conduct a thorough review of these data or

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relationships (e.g. second hand smoking and lung cancer) . . . where the strength of association is in the order of 20-40%.") (endnote omitted).)

[109] (Moorman Rep. at 13 (citing Taylor et al., *Meta-analysis of studies of passive smoking and lung cancer: effects of study type and continent*, 36 Int'l J. Epidemiol. 1048 (2007) ("Taylor 2007") (attached as Ex. A138 to Tersigni Cert.)).)

the data supporting the other associations she identifies.[110] And Dr. Moorman completely ignores that the Taylor study reported: (1) nearly identical results between cohort studies and both types of case-control studies (each type collectively showing a similar and statistically significant positive association); and (2) a clear dose-response relationship.[111]

Dr. Moorman and her colleagues also failed to consider whether stronger evidence supported causal inferences for the other associations they discuss. For example, as Dr. Diette explains, the association between hormone therapy drugs and breast cancer was demonstrated by controlled clinical trials (i.e., the highest form of scientific evidence).[112]

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110 (Moorman Dep. 253:19-255:11, 259:19-260:19.)

111 Taylor 2007 at 1051 tbl. 4, 1052 (reporting statistically significant relative risks of 1.22 for seven cohort studies, 1.18 for 25 population-based case-control studies and 1.33 for 23 non-population-based case-control studies; further reporting that 20 of 36 studies reporting dose-response data showed a statistically significant trend); *see also* Brennan et al., *Secondhand Smoke Exposure in Adulthood and Risk of Lung Cancer Among Never Smokers: A Pooled Analysis of Two Large Studies*, 109 Int'l J. Cancer 125, 125 (abstract) (2004) (attached as Ex. A14 to Tersigni Cert.) (finding that the data on second-hand smoking and lung cancer demonstrate a "[c]lear dose response"). Second-hand smoke is also different from talc use because it is well accepted that smoking causes lung cancer. Second-hand smoke is a less direct way of being exposed to a known carcinogen, whereas talc use involves exposure to a substance that is not generally accepted as harmful.

112 (Diette Rep. at 23.)

The fact that the other causal determinations plaintiffs' experts cite were based on different (and stronger) data renders them irrelevant and unsupportive of plaintiffs' experts' causation opinions. *See McClain*, 401 F.3d at 1245 (expert's failure to "show the reliability of each of his steps in deducing Metabolife's toxicity from [an] analogy" to a different drug was "a fatal defect under *Daubert*"); *Henricksen v. ConocoPhillips Co.*, 605 F. Supp. 2d 1142, 1164-65 (E.D. Wash. 2009) (excluding expert opinion where expert was unable to "demonstrate a scientifically valid basis for projecting the findings of a study to the proffered causal theory"); *Burst v. Shell Oil Co.*, No. 14-109, 2015 WL 3755953, at *16 (E.D. La. June 16, 2015) (excluding expert testimony for "rel[ying] on a universe of divergent studies that either did not examine the substance at issue, [or] did not examine the disease at issue").

For all of these reasons, the strength of association consideration is not met and does not support a causal inference, and plaintiffs' experts' opinions to the contrary are unreliable.

### B. Plaintiffs' Experts Use Unreliable Methodologies To Conclude That The Studies Are Consistent.

The consistency prong of Bradford Hill asks whether the association "[h]as been repeatedly observed by different persons, in different places, circumstances and times."[113]

Plaintiffs' experts' opinions that consistency of association weighs "significantly" in favor of causation are based on a blatant distortion of the scientific evidence.[114] Unless "consistency" is understood to mean its opposite, plaintiffs' experts' opinions are irreconcilable with the fact that only half of the population-based case-control studies show a weak or modest statistically significant association between perineal talc use and ovarian cancer, and ***none*** of the cohort studies or hospital-based case-control studies shows such an increase.

Consistency of association means that "[d]ifferent studies that examine the same exposure-disease should yield similar results,"[115] and that an observed association should be "repeatedly observed by different persons, in different places,

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113 Hill 1965 at 296.

114 (McTiernan Rep. at 64-65; Singh Rep. at 63; *see also* Carson Rep. at 9; Clarke-Pearson Rep. at 7-8; Kane Rep. at 34; Moorman Rep. at 29; Siemiatycki Rep. at 64; Smith Rep. at 20; Smith-Bindman Rep. at 38, 41; Wolf Rep. at 14-15 (all similar).)

115 Epidemiology Reference Manual at 604.

circumstances and times."[116] Here, not only have "different studies" conducted under different "circumstances" not shown an increased risk, but the studies that the epidemiological community ***regards as more reliable*** have failed to find any association.[117] This is particularly concerning because the most reasonable explanation for the inconsistency between case-control and cohort studies is that the former are reporting false positives due to recall bias and/or confounding, as discussed above (*see* pp. 23-25).

Plaintiffs' experts mostly ignore the inconsistency between cohort and case-control studies,[118] or brush the cohort studies aside as flawed and irrelevant.[119] But

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116 Hill 1965 at 296.

117 Although IARC stated in 2010 that the risk reported in studies of ovarian cancer and talc is "unusually consistent," only one cohort study had been published at the time. *See* IARC 2010 Monograph at 412. As set forth above, there have now been three additional cohort studies, which have each failed to find an association between perineal talc use and ovarian cancer.

118 (*See, e.g.*, Smith Rep. at 16 (opining that there is a consistency of association based only on case-control studies and meta-analyses); Wolf Rep. at 8 ("Results are generally consistent across case-control, meta-analysis, and pooled analysis studies.") (citation omitted); Wolf Rep. at 15 ("Results are generally consistent across case-control, meta-analysis, and pooled analysis studies."); Carson Rep. at 8 ("Most, but not all, of these studies show a consistent positive relationship."); Kane Rep. at 9 (opining "there is general consistency") (citation omitted).) Dr. Clarke-Pearson does not even discuss the cohort studies in his report other than to note that they "are compelling." (Clarke-Pearson Rep. at 7.)

119 (*See, e.g.*, McTiernan Rep. at 64 (arguing that case-control studies are consistent and that the "more attenuated" results from cohort studies "do not negate the significant case-control study findings"); Singh Rep. at 17 (finding

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courts have recognized that experts cannot manufacture consistency under a Bradford Hill analysis by simply ignoring an entire category of relevant studies.

In *Carl*, for example, Judge Johnson excluded the opinions of two plaintiffs' experts who "looked askance upon the three large cohort studies presented by [d]efendants," which did not identify an association between talc use and ovarian cancer, and instead relied only on case-control studies favorable to their causation opinions.[120] 2016 WL 4580145, at *12, *19. As the court explained, the plaintiffs' experts' "rigidly dismissive" approach to cohort studies was unreliable, especially in light of the accepted understanding that case-control studies are generally "less reliable than a prospective cohort study." *Id.* at *19. Other courts have ruled similarly. *See In re Zoloft (Sertraline Hydrochloride) Prods. Liab. Litig.*, No. 12-md-2342, 2015 WL 7776911, at *10 (E.D. Pa. Dec. 2, 2015) ("*Zoloft II*") (excluding expert whose "selective emphasis on trends and general consistency

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"evidence of consistency" in part because "[t]he number of ovarian cancers in the case-control studies exceeds the number of ovarian cancers in the cohort studies"); Smith-Bindman Rep. at 38 (arguing that there is consistency because studies collectively show a roughly 40% increased risk, ignoring that cohort studies show no increased risk).)

120 Those experts, Drs. Daniel Cramer and Graham Colditz, have apparently been abandoned by plaintiffs in light of Judge Johnson's ruling, but several of plaintiffs' experts rely on Dr. Cramer's studies as supposed support for their positions.

only when such concepts support his opinion is one example of 'situational science' which renders his opinion unreliable"), *aff'd*, *Zoloft III*, 858 F.3d 787.

Here, too, plaintiffs' experts are "rigidly dismissive" of cohort studies in their consistency analyses. And while they have imagined several bases for ignoring cohort studies in these analyses, their justifications all lack scientific support.

1. Plaintiffs' Experts Advance Unreliable Arguments In An Effort To Minimize The Significance Of The Relevant Cohort Studies.

Plaintiffs' experts advance a number of arguments in an attempt to explain away the fact that cohort studies examining perineal talc use have not shown an increased risk of ovarian cancer, but these arguments are scientifically unsound and should be disregarded. *See Zoloft III*, 858 F.3d at 800 ("Claiming a consistent result without meaningfully addressing" studies finding no significant association "undermines reliability").

***Size And Power Of Cohort Studies.*** One of plaintiffs' experts' primary arguments is that cohort studies do not show a statistically significant association because they did not follow a sufficient number of women who developed ovarian

cancer – i.e., that the cohort studies lack sufficient statistical power.[121] This argument fails on its own logic.

A recent meta-analysis specifically considered whether low statistical power could explain the fact that talc cohort studies show negative results and rejected that theory, concluding: "[T]he statistical power of the meta-analysis of these cohort studies to detect a RR of 1.25, similar to the result of the meta-analysis of case-control studies, was 0.99. Thus, ***low power of cohort studies cannot be invoked as [an] explanation of the heterogeneity results***."[122] Several of plaintiffs' experts testified that they do not dispute the validity of the peer-reviewed Berge calculation – yet they still place more weight on case-control studies based on the erroneous premise that the cohort studies are underpowered.[123]

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[121] (*E.g.*, McTiernan Rep. at 46-48; Smith Rep. at 20; Carson Dep. 251:17-253:3; Moorman Rep. at 24-25; Siemiatycki Rep. at 15-16; Singh Rep. at 16; Wolf Rep. at 6.)

[122] Berge 2018 at 253 (emphasis added). (*See also* Merlo Rep. at 33 (conducting similar power calculation and reaching the same conclusion).) The 0.99 figure means that "there would be a 1% chance of being incorrect and concluding that there is no difference in risk of ovarian cancer between participants exposed and unexposed to talc if there was a true increase in risk of ovarian cancer with talc exposure." (Merlo Rep. at 37.)

[123] (*E.g.*, Moorman Dep. 215:17-23; Dep. of Judith Wolf, M.D. ("Wolf Dep.") 261:23-262:9, Jan. 7, 2019 (attached as Ex. B30 to Tersigni Cert.); Singh Dep. 157:14-18, 159:6-160:1.)

Although Dr. McTiernan conducted her own analysis of statistical power in an effort to discredit the cohort studies, and several other witnesses rely on a similar calculation set forth in a commentary by Narod,[124] those calculations actually show that the cohort studies ***do*** have sufficient statistical power. Dr. McTiernan calculates that studies need to have 931 ovarian cases to detect a statistically significant relative risk of 1.3,[125] and Narod calculates that studies need at least 200,000 total participants to detect a statistically significant relative risk of 1.2.[126] Even if these calculations were correct (and Dr. Merlo explains why they are not),[127] the talc cohort studies collectively studied almost ***1,400 women*** who developed ovarian cancer and more than 200,000 who did not, easily surpassing these supposed thresholds.[128] Thus, the cohort studies had the power to detect a

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124 (*See* Moorman Rep. at 25; Smith Rep. at 20; Wolf Rep. at 6.)

125 (McTiernan Rep. at 48.)

126 Narod, *Talc and Ovarian Cancer,* 141(3) Gynecol. Oncol. 410, 411 (2016) (attached as Ex. A97 to Tersigni Cert.).

127 As Dr. Merlo explains, these calculations are incorrectly based on the incidence of ovarian cancer in the general population; when studies are restricted to higher-risk population segments, as the cohort studies were (because they focused on older women, who have a much higher risk of disease), smaller samples can detect increased risk. (Merlo Rep. at 37-38.)

128 (*See* McTiernan Dep. 219:19-220:10 (acknowledging that the cohort studies collectively included 1,372 ovarian cancer cases); Wolf Dep. 256:3-18 (testifying that the cohort studies collectively studied more than 200,000 women, surpassing the Narod cutoff).) *See also* Gates 2010 at 47, 48 tbl. 1 (reporting 108,073 non-cases for NHS and 112,869 non-cases for NHSII, 797 ovarian cancer cases for

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statistically significant risk if it existed – and their failure to do so precludes a finding of consistency.

***Disease Latency And Study Follow-Up.*** Plaintiffs' experts also criticize the cohort studies for having supposedly insufficient follow-up periods given the putative latency period of ovarian cancer.[129] This argument is speculative and circular for several reasons.

For one thing, the latency argument depends on the unsubstantiated premise that ovarian cancer takes at least 20 years to develop; yet, even plaintiffs' witnesses concede that a precise latency period for ovarian cancer has not been established and offer wildly divergent guesses as to what any latency period might

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NHS and 127 ovarian cancer cases for NHSII); Houghton 2014 at 2 (reporting 61,576 participants with 429 ovarian cancer cases); Gonzalez 2016 at 797 (reporting 41,654 participants with 154 ovarian cancer cases). The Gonzalez study was published in November 2016, months after the Narod editorial was finalized in April 2016; thus, Narod did not account for the additional 50,884 participants in the Gonzalez study. The fact that plaintiffs' experts argue that cohort studies are underpowered via the Narod calculation is further evidence that they have haphazardly and uncritically assessed the literature.

[129] (*E.g.*, McTiernan Dep. 226:20-227:17 (criticizing cohort studies for "not follow[ing] the women for very long"); Siemiatycki Dep. 169:19-172:6 (testifying that, among other biases, "short follow-up periods . . . would be a source of bias in cohort studies"); Wolf Rep. at 8 (similar).)

be.[130] And any conclusion that there is a latency period between talc exposure and ovarian cancer is even more speculative because there is no evidence that talc exposure causes ovarian cancer in the first place.[131]

In any event, the notion that cohort studies reflect only limited spans of talc use is likewise incorrect. For one thing, Gates 2010 actually followed women for 24 years, longer than plaintiffs' claimed latency period.[132] Although some of the cohort studies studied women for less than 20 years (for example, the Houghton study followed women for 12.5 years), nothing in these studies suggests that the study populations' use of talc began at the same time as the study.[133] The contrary assumption is far more reasonable – that most study participants began talc use

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130 (Singh Dep. 171:3-6 ("I don't know a specific number. It's, you know, several years"); Carson Dep. 168:7-9 (testifying that the latency period for ovarian cancer is 20-40 years); Wolf Dep. 325:23-327:4 (testifying that the latency period could be 15 to 20 years, but she "d[idn't] know the latency period for sure"); Clark-Pearson Dep. 52:8-22 (unable to be more precise about latency than "decades of exposure").)

131 *See* Fiume 2015 at 117S (positing that "no studies have characterized . . . the latency of purported talc-induced ovarian cancer"); *see also* Hanchette et al., *Ovarian Cancer Incidence in the U.S. and Toxic Emissions from Pulp and Paper Plants: A Geospatial Analysis*, 15 Int'l J. Envtl. Res. Pub. Health 1619, 1619 (2018) (attached as Ex. A54 to Tersigni Cert.) (noting that latency period for ovarian cancer is unknown). (*See also* Diette Rep. at 11.)

132 Gates 2010 at 50 tbl. 4.

133 Notably, the Houghton study queried participants about length of use, and it expressly reported that perineal use of talcum powder for "20 or more years was not associated with increased risk of ovarian cancer compared with never users." Houghton 2014 at 3.

prior to the study, years or decades before. (*See* Merlo Rep. at 39 ("the women followed in all of these studies presumably did not start using talc for the first time the day the studies began and therefore would have had longer durations of use than the time period of the study – in most cases many years more").) As studies have shown (and even plaintiffs' witnesses have admitted), "ever users" of talc average at least 20 years of talc use, and women typically begin using talcum powder by age 20.[134] In short, a substantial number of cohort study participants

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[134] Wu et al., *African Americans and Hispanics Remain at Lower Risk of Ovarian Cancer Than Non-Hispanic Whites after Considering Nongenetic Risk Factors and Oophorectomy Rates*, 24(7) Cancer Epidemiology Biomarkers Prev. 1094, 1097 tbl. 2 (2015) ("Wu 2015") (attached as Ex. A155 to Tersigni Cert.) (reporting mean talc use of more than 20 years for all groups for both cases and controls); Cramer et al., *The association between talc use and ovarian cancer: a retrospective case-control study in two US states*, 27 Epidemiology 334, 335 (2016) ("Cramer 2016") (attached as Ex. A25 to Tersigni Cert.) (reporting that the "average age women began using talc was 20.0 for cases and 19.8 for controls" in population-based study of 3,957 women diagnosed with ovarian cancer in eastern Massachusetts and New Hampshire); IARC 2010 Monograph at 205 ("The use of talcum powder for feminine hygiene is acquired in young adulthood, since 80% of women who use body powder start before the age of 25 years . . . ."); Harlow 1992 at 21 tbl. 2 (indicating that 81.6% of cases and 80.9% of controls who reported age of first use of talc responded that they were age 25 or younger); Gates et al., *Talc use, variants of the GSTM1, GSTT1, and NAT2 genes, and risk of epithelial ovarian cancer*, 17(9) Cancer Epidemiol. Biomarkers Prev. 2436, 2443 (2008) ("Gates 2008") (attached as Ex. A43 to Tersigni Cert.) ("[A]pproximately 95% of controls with a history of regular genital talc use reported first using talc before age 35 years."). (*See also* Singh Dep. 165:2-8 (recognizing these figures); Wolf Dep. 320:16-321:1 (same); Clarke-Pearson Dep. 167:24-168:2 (same).)

would have been using talcum powder for decades before the follow-up periods even began, putting to rest any scientifically-grounded concerns about latency.

***Ascertainment Of Talc Exposure.*** Plaintiffs' witnesses additionally criticize the cohort studies for supposedly failing to accurately ascertain enrollees' talc use for various reasons, principally that they did not ask sufficiently specific questions about talc use to gather meaningful exposure data[135] and potentially misclassified participants as talc users or non-talc users because they did not repeatedly update survey data on talc use.[136] These criticisms are unreliable because plaintiffs' experts do not apply them evenhandedly.

As several defense experts explain,[137] the inability to accurately measure how much talc a woman uses is a limitation of ***both*** cohort and case-control studies. And plaintiffs' experts do not provide any basis to conclude that the case-control studies captured women's talc exposure more accurately, rendering their opinions pure *ipse dixit*. *See, e.g.*, *Gen. Elec. Co. v. Joiner*, 522 U.S. 136, 146 (1997) (expert opinions inadmissible if connected to data only by *ipse dixit* of expert); *Soldo*, 244 F. Supp. 2d at 527 ("When an expert's testimony 'relies in part on his

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135 (*See* McTiernan Rep. at 46; Smith Rep. at 16.)

136 (Smith-Bindman Rep. at 19; Singh Rep. at 11-12.)

137 (Diette Rep. at 32; Merlo Rep. at 26-27.)

own *ipse dixit*, rather than on something more readily verifiable . . . it is open to attack.'") (citation omitted).[138]

Any concern that talc users and nonusers are misclassified in cohort studies in a way that artificially reduced relative risks is likewise speculative. This argument requires an assumption that many participants in cohort studies initially reported that they did not use talc, but later became talc users. Such usage patterns are highly improbable in light of the studies that have reported that most talc users begin using talc by their mid-20s (the average age of women at the end of each cohort study was over 50) and that the mean duration of talc use is greater than 20 years.[139]

***Arguments Regarding Gates 2010.*** Finally, plaintiffs' witnesses specifically criticize the Gates 2010 study – which reported no association between talc use and HGSOC (or any other subtypes of ovarian cancer) after 10 years of

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[138] Plaintiffs' experts' exposure-measurement argument is primarily directed at attempting to explain why cohort studies do not show a dose response – i.e., they contend that cohort studies might correctly determine whether or not participants ever used talcum powder, but that too many did not ask the right questions about how frequently talc was used and for how long. In so arguing, plaintiffs' experts ignore that numerous studies that have measured "cumulative" talc use (plaintiffs' experts' preferred means of measuring talc dose) have ***not*** shown a dose response, as discussed further below (*see* pp. 71-73).

[139] *See, e.g.*, Wu 2015 at 1097 tbl. 2 (showing mean talc use of more than 20 years across all groups); IARC 2010 Monograph at 305 (positing that 80% of talc users begin by age 25).

additional follow-up from the Gertig 2000 study. Specifically, plaintiffs' experts argue that Gates 2010 should be disregarded because it did not: (1) update data on participants' talc use beyond the baseline assessment in Gertig 2000;[140] or (2) use the same talc usage categories as Gertig 2000 to evaluate the risk of HGSOC.[141] While every observational study has limitations, these limitations do not invalidate the validity of the Gates findings.

As an initial matter, plaintiffs' experts cannot dispute that the additional decade of follow-up provided by the Gates 2010 study provides valuable data; indeed, arguing otherwise would contradict their general contention that the cohort studies did not follow participants long enough. Moreover, plaintiffs' experts have not provided any reason to believe that relying on the baseline talc use data from Gertig 2000 made the Gates 2010 results inaccurate. For one thing, if women who initially used talc stopped during the ten years of additional follow-up provided by the Gates study, they would still have used talc at some point during the cohort period and would properly be considered "ever" talc users. And in any event, the

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140 (*See, e.g.*, Singh Dep. 164:16-23; Moorman Dep. 190:4-24; McTiernan Dep. 224:3-7; Smith-Bindman Rep. at 20.)

141 (McTiernan Rep. at 45-46 (arguing that the two studies cannot be compared because Gertig 2000 reported on ever/never use and Gates 2010 combined "never use" and "less than once per week" into one referent category); Siemiatycki Rep. at 61 (Gates 2010 "almost certainly suffered from an attenuated RR estimate because of the compromised reference category of 'unexposed'").)

evidence suggests that study participants are unlikely to have changed their use habits because, as noted above: (1) most women start talc use by their mid-20s (and thus would not be expected to switch categories in the Nurses' Health Study, which enrolled women between the ages of 30 and 55); and (2) women use talc on average for more than 20 years (meaning it is also unlikely that many women would have ceased using talc midway through the study).[142] Accordingly, even if the lack of additional questioning on talc use is a weakness of the Gates study (as the authors acknowledge), it is not a reason to exclude the study from the causation analysis.[143] As Dr. Diette explains, "even though the participants were only asked about their talcum powder use once, the data collected on perineal talcum powder application would have likely reflected chronic, habitual use."[144]

The use of different comparators is also not a scientifically sound reason to reject the Gates 2010 study. For one thing, in their 2008 nested case-control study (a case-control study using data from the Nurses' Health Study cohort), the Gates authors provided an explanation for their categorization of talc use, explaining that

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142 *See* Gertig 2000 at 249 (noting ages on enrollment and date of talc use ascertainment); Wu 2015 at 1097 tbl. 2 (mean talc use of more than 20 years); IARC 2010 Monograph at 305 (80% of talc users begin by age 25).

143 (Smith-Bindman 2/8/19 Dep. 343:8-12; *see also* McTiernan Dep. 187:22-188:9 (arguing that it was reasonable for Penninkilampi 2018 to exclude Gates 2010).)

144 (Diette Rep. at 10.)

their "assumption [was] that habitual use is more likely to be associated with ovarian cancer" and "likely to be recalled more accurately than sporadic use."[145] Moreover, a number of plaintiffs' experts hypothesize that a certain threshold of talc exposure must be exceeded before there is a risk of ovarian cancer.[146] If this were true, any association would be better captured by the comparison used in the Gates study (which grouped never users and "less than once per week" users in a single, low-exposure category). As Dr. Ballman explains, "If there is a threshold effect, as has been put forward by some of plaintiffs' experts, then grouping no use with infrequent use should better detect an association because placing the infrequent users with regular users would make the association weaker if infrequent use is not above the threshold value."[147]

Finally, it is worth noting that in their 2008 nested case-control study, Gates et al. separately broke out the data for never users from three different subgroups of ever users, one of which was "[l]ess than once a week" users.[148] None of the three categories of ever users had a statistically significant increase in risk for

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145 Gates 2008 at 6, 8.

146 (*E.g.*, Clarke-Pearson Rep. at 9; Wolf Rep. at 14-15; McTiernan Rep. at 14; Siemiatycki Rep. at 15; Singh Rep. at 18; Smith-Bindman Rep. at 40.)

147 (Ballman Rep. at 48.)

148 Gates 2008 at 6 tbl. 3.

epithelial or serous invasive ovarian cancer over never users.[149] In other words, the change in categorization clearly is not the reason why the association for HGSOC disappeared upon further follow-up of the NHS participants.

2. Plaintiffs' Experts Improperly Disregard Statistical Significance In Reaching Their Conclusions On Consistency.

Finally, in an effort to bolster their claims that the epidemiological data are consistent, plaintiffs' experts attack the long-established concept of statistical significance as "irrelevant" and obsolete.[150] This categorical dismissal of statistical significance further renders their opinions unreliable.

The Third Circuit addressed the importance of statistical significance in *Zoloft III*, 858 F.3d at 793-94, 799. There, the court "decline[d] to state a bright-line rule" as to "whether statistical significance is necessary to prove causality,"

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149 *Id.*

150 (*E.g.*, Siemiatycki Rep. at 64 (stating that he is "impressed by the consistently elevated risk across studies" because "[a]lmost all of the 30 or so studies have produced an RR greater than the null (neutral) value of 1.0"; it is "irrelevant" that "individual study RRs are not all necessarily statistically significant"); McTiernan Rep. at 41-42, 44 (opining that "8 studies did not have statistically significant results, [but] provide relevant data because their relative risk estimates were consistent with the 16 studies that showed statistically significant results" and that the results of cohort studies, "while not statistically significant, are consistent with an association between" talc use and ovarian cancer); Singh Rep. at 63 (finding consistency because "nearly all point estimates show[] a direction of increased risk of ovarian cancer"); Plunkett Rep. at 49 (finding consistency because the non-statistically significant findings "often" reported "a trend towards an increased risk in women who used talcum powder products").)

but maintained that statistical significance is "an important metric to distinguish between results supporting a true association and those resulting from mere chance." *Id.* at 793. The court ultimately affirmed exclusion of an expert who inappropriately "classified insignificant odds ratios above one as supporting a 'consistent' causality result, downplaying the possibility that they support *no* association." *Id.* at 799. In so ruling, the court explained that "[w]hile an insignificant result *may* be consistent with a causal effect," the expert's approach was "too far-reaching" and "understat[ed] the importance of statistical significance." *Id.* The Third Circuit's ruling is consistent with a decision last year by the Fourth Circuit, which affirmed the exclusion of Dr. Singh's general causation opinion regarding the drug Lipitor because the plaintiffs "failed to demonstrate that Dr. Singh's reliance on non-statistically significant 'trends' is accepted in [the] field" or has "served as the basis for any epidemiologist's causation opinion in peer-reviewed literature." *In re Lipitor (Atorvastatin Calcium) Mktg., Sales Practices & Prods. Liab. Litig.*, 892 F.3d 624, 641-42 (4th Cir. 2018) (citation omitted); *see also Bracco Diagnostics, Inc. v. Amersham Health, Inc.*, 627 F. Supp. 2d 384, 452 (D.N.J. 2009) (Wolfson, J.) (excluding expert who rejected the generally accepted practice of using p-values to test for statistical significance; the expert's position "regarding the use of the p-value is not properly based upon science and is not reliable").

Plaintiffs' experts have committed the same methodological errors here. Dr. Siemiatycki, for example, attests that the consistency consideration is satisfied because the majority of studies have "produced an RR greater than . . . 1.0."[151] But that conclusion holds only if the statistical significance of those findings is entirely ignored. Thus, just as in *Zoloft*, plaintiffs' experts' approach is "too far-reaching" because it "understat[es] the importance of statistical significance" and "downplay[s] the possibility that [the insignificant positive results] support *no* association." *Zoloft III*, 858 F.3d at 799.

Plaintiffs' attack on statistical significance was also evident at the depositions of defendants' experts, where plaintiffs' counsel asked numerous questions about a "Comment" (co-authored by one of their consulting experts) that was recently published in the journal *Nature*, "call[ing] for the entire concept of statistical significance to be abandoned."[152] But the practices under attack in the Amrhein commentary – in essence, treating statistical significance as dispositive of every study, regardless of context – have no bearing here. Defendants are not

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[151] (Siemiatycki Rep. at 64; *see also* Carson Dep. 110:18-111:10; McTiernan Rep. at 41-42; Moorman Dep. 262:9-25; Singh Dep. 117:6-22.)

[152] Amrhein et al., *Retire statistical significance*, 567 Nature 305, 306 (Mar. 21, 2019) ("Amrhein 2019") (attached as Ex. A8 to Tersigni Cert.). Sander Greenland, one of three co-authors of the "Comment," was disclosed as a consulting expert for plaintiffs. (Pls.' Steering Committee's Initial Designation & Disclosure of Non-Case Specific Expert Witnesses at 6 (attached as Ex. I3 to Tersigni Cert.).)

arguing that positive yet insignificant results should be ignored altogether – only that, consistent with the *Zoloft* decision, blindly counting such studies as affirmative evidence of consistency of association commits the same kind of error at the opposite extreme. Notably, the Amrhein proposal expressly did "not advocat[e] a ban on *P* values, confidence intervals or other statistical measures – only that we should not treat them categorically"; nor did it "***advocat[e] for an anything goes situation, in which weak evidence suddenly becomes credible***."[153]

Moreover, *Nature*'s editorial board clarified in its preface that it has no plans to "change how [the journal] considers statistical significance."[154] In short, the commentary's recommendations are largely consistent with defendants' position and, to the extent they are not, the recommendations have not gained general scientific acceptance.[155]

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153 Amrhein 2019 at 306 (emphasis added).

154 *See Significant debate*, 567 Nature 283 (Mar. 21, 2019) (attached as Ex. A132 to Tersigni Cert.).

155 Not surprisingly, the controversial proposal to "retire statistical significance" has been heavily criticized in the scientific community. *See, e.g.*, Johnson, *Retiring significance: raise the bar*, 567 Nature 461 (2019) (attached as Ex. A81 to Tersigni Cert.) (explaining that results that are barely statistically significant often "provide evidence supporting the null hypothesis of no association" when carefully examined) ; Ioannidis et al., *The Importance of Predefined Rules and Prespecified Statistical Analyses: Do Not Abandon Significance*, JAMA Online (2019), https://jamanetwork.com/journals/jama/fullarticle/2730486 (attached as Ex. A79 to Tersigni Cert.) (explaining that objective pre-defined standards like statistical significance remove

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Plaintiffs' experts generally argue that the reason they can ignore statistical significance is that studies that reported insignificant results only did so because they lacked adequate power.[156] This argument echoes their unsupported critique of the power of the cohort studies, and it is just as unreliable. Specifically, plaintiffs' experts posit that insignificant results from different studies may be combined.[157] But in so arguing, they ignore the fact that, when combined, the cohort studies ***continue to yield a non-statistically significant relative risk that is barely above***

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"leeway to manipulate the data and hack the results to claim important signals" and that without such standards, "science and policy may rely less on data and evidence and more on subjective opinions and interpretations").

[156] (*E.g.*, Siemiatycki Rep. at 64 (lack of statistical significance "is irrelevant because most individual studies did not have sufficient statistical power to detect RR in the range of 1.2-1.4"); McTiernan Rep. at 45 (arguing that cohort study's "lack of statistical significance is likely due to [its] insufficient sample size"); Moorman Rep. at 25 ("the lack of a significant overall association between ever use of talc and ovarian cancer in the cohort studies may be due to the fact that the [sic] despite the large size of the cohorts, the studies were not adequately powered to detect a relative risk of approximately 1.2").)

[157] (*See* Siemiatycki Rep. at 64 ("It is the statistical significance of the meta-RR, representing the ***combined evidence*** that has the requisite power, and that excess RR is highly statistically significant." (emphasis added)); Smith Dep. 290:4-20 (agreeing that "[i]ndividually" "there is an inconsistency between the results by the cohort studies as compared to the results produced by the case control studies," but arguing that "when they go into the whole stew pot it becomes statistically significant and consistent"); *see also* § I.B.1, *supra*.)

***1.0***, which cannot be attributed to a lack of power, as explained above.[158] Accordingly, even adopting plaintiffs' experts' approach of aggregating insignificant results, the fundamental problem of inconsistency between the results of cohort studies and case-control studies remains, rendering any opinion that these sets of studies somehow evince consistency entirely unreliable. *See Zoloft III*, 858 F.3d at 799 (explaining that it was unreliable for an expert to consider insignificant results from a larger study consistent with significant results from smaller studies).[159]

For all of these reasons, the consistency of association factor does not support a conclusion that causation has been established, and plaintiffs' experts' arguments to the contrary are unreliable.

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[158] *See* Berge 2018 at 6-7 & fig. 2 (combined RR 1.02 (0.55-1.20)). (*See also* § I.B.1, *supra*.)

[159] Several of plaintiffs' experts also opine that consistency is satisfied because the talc meta-analyses have consistently reported an aggregate relative risk of roughly 1.2-1.3 (*e.g.*, Clarke-Pearson Rep. at 8; Smith Rep. at 20; Wolf Rep. at 14-15), but consistency among meta-analyses is not remarkable or meaningful. As Dr. Saenz explains, "[t]his is not consistency; it is simply repetition" because the meta-analyses "dr[e]w from many of the same" underlying studies. (Saenz Rep. at 24 & tbl. 2; *accord id.* at 16-17.) Moreover, gleaning a supposed consistency of association from the talc meta-analyses is problematic because meta-analyses are generally "subject to the same weaknesses and biases that were embedded in the smaller original studies" – i.e., the bias and confounding issues, which, as explained above, could account for the small association reported in case-control studies. (*Id.* at 16.) *See also E.R. Squibb & Sons, Inc.*, 1990 U.S. Dist. LEXIS 15788, at *41-42 (acknowledging theoretical utility of meta-analysis but rejecting use of one that included a poor-quality study).

### C. Plaintiffs' Experts' Opinion That The Epidemiological Studies Show A Dose Response Contradicts Scientific Consensus And Defies The Evidence.

Plaintiffs' experts also attempt to extract evidence of a dose response from a subset of studies (and even from subsets of data within these cherry-picked studies), even though the body of data clearly does not show a dose response.[160] This too is an unreliable approach to Bradford Hill.

Dose response is considered by some to be the "single most important factor to consider in evaluating whether an alleged exposure caused a specific adverse effect." *McClain*, 401 F.3d at 1242 (citation omitted); *see also Chapman v. Procter & Gamble Distrib., LLC*, 766 F.3d 1296, 1308 (11th Cir. 2014) (a dose response is "indispensable to proving the effect of an ingested substance" and "establish[ing] general causation"); *Newman v. Motorola, Inc.*, 218 F. Supp. 2d 769, 778 (D. Md. 2002) (excluding causation expert in part because of the "lack of any demonstrated dose-response relationship" between cell phone use and brain cancer), *aff'd*, 78 F. App'x 292 (4th Cir. 2003) (per curiam); *Amorgianos v. Nat'l*

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[160] Unsurprisingly given the dearth of data demonstrating a dose response, plaintiffs' experts assign a range of weights (or lack thereof) to this factor. (*Compare, e.g.*, McTiernan Rep. at 66 ("significant" evidence of a causal relationship), *and* Siemiatycki Rep. at 63 (referring to dose response as "an important consideration in my assessment of causality"), *with, e.g.*, Smith Rep. at 20 (additional research needed to "help clarify dose response relationships"), *and* Clarke-Pearson Rep. at 9 (calling for molecular research to "elucidate" dose response).)

*R.R. Passenger Corp.*, 137 F. Supp. 2d 147, 188 (E.D.N.Y. 2001) (excluding general causation expert who cited literature in which "[f]ew, if any, dose-response relationships were reported"), *aff'd*, 303 F.3d 256 (2d Cir. 2002); *Soldo*, 244 F. Supp. 2d at 515 (excluding experts where "[n]o dose response relationship for Parlodel and the occurrence of Intracerebral hemorrhage ha[d] been documented") (citation omitted).

Here, the scientific consensus is that a dose response has ***not*** been established between talc use and ovarian cancer – as pronounced by plaintiffs' experts outside the litigation context, as well as by public health authorities.[161] Even a number of plaintiffs' experts concede that there is weak, if any, evidence of a dose response, variously opining that the relevant evidence is "equivocal,"

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[161] *See, e.g.*, Langseth 2008 at 359 (meta-analysis co-authored by Dr. Siemiatycki explaining that a crucial missing piece of causation evidence was "***the absence of clear exposure-response associations in most studies***.") (emphasis added); FDA Denial Letter at 4 (arguing that "dose-response evidence ***is lacking***") (emphasis added); 2019 NCI PDQ (reporting that "a dose response relationship was not found" and "there was no increased risk observed for increasing duration of use"); IARC 2010 Monograph at 412 ("inconsistent" evidence of a dose response). Notably, the Health Canada Draft Screening Assessment that has been touted (and potentially influenced) by plaintiffs and their experts reported that "[t]here is a lack of an available exposure-effect relationship in the human epidemiological data"; that "a relationship between the concentration/dose of talc in the powder and the incidence of ovarian cancer could not be investigated"; and that even among "studies that provided some evidence of increased risk of ovarian cancer with increasing perineal applications of talc," "***none demonstrate both a clear dose-response trend and statistical significance***." Draft Screening Assessment at 20-21 (emphasis added).

"inconsistent," "less compelling" and should be "given [] lesser weight" in the causation analysis.[162]

Nevertheless, several of these same experts consider the weak evidence of a dose response to be strongly supportive of causation.[163] These contradictions

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[162] (*See, e.g.*, Kane Rep. at 35 ("equivocal"); Singh Rep. at 65 ("less compelling"); Smith-Bindman Rep. at 40 ("inconsistent"); Wolf Rep. at 15 ("less important factor"); *see also* Saed Rep. at 11 (observing that the epidemiological studies "have shown conflicting results regarding the presence of a dose-response, largely due to the failure of many studies to obtain necessary information on the frequency and duration of usage and the inherent challenge of quantifying actual exposure"); Siemiatycki Dep. 123:8-14 (agreeing that the data are "compatible with no dose-response relationship"; "it could be a chance finding").)

[163] (Kane Rep. at 35 (the "equivocal" "evidence of biological gradient supports cause and effect" and "was an important factor in my analysis"); Singh. Rep. at 65 (the "less compelling" evidence of a dose response is "still compelling [support] of my causation analysis"); *see also* McTiernan Rep. at 65 ("I placed significant weight on this factor . . . ."); Siemiatycki Rep. at 63 (an "important consideration in my assessment of causality"); Plunkett Rep. at 50, 52 (finding, among data that support causation, that "there are sufficient scientific data supporting the existence of a dose-response relationship").) Drs. McTiernan, Siemiatycki and Plunkett all contradict their peers and argue that there is strong evidence of a dose response. But the epidemiological studies they point to (i.e., cherry-picked studies such as the Terry 2013 study) are not reliable evidence of dose response, as set forth below. Dr. Plunkett additionally claims that "in vitro and animal study data" demonstrate a dose response (Plunkett Rep. at 50), but the studies she cites (Buz'Zard & Lau, *Pycnogenol reduces Talc-induced Neoplastic Transformation in Human Ovarian Cancer Cultures*, 21 Phytotherapy Res. 579 (2007) (attached as Ex. A16 to Tersigni Cert.), and Shukla et al., *Alterations in Gene Expression in Human Mesothelial Cells Correlate with Mineral Pathogenicity*, 41 Am. J. Respiratory Cell Molecular Biology 114 (2009) (attached as Ex. A131 to Tersigni Cert.), among others) are inapposite, as explained in Defendants' Memorandum of Law in Support of Motion to Exclude Plaintiffs' Experts' Opinions Related to Biological Plausibility ("Biological Plausibility Brief").

demonstrate an unreliable methodology; as courts have recognized, the lack of a clear dose response is actually strong evidence ***against*** causation, not merely "less compelling" evidence in support of it. *See, e.g.*, *McClain*, 401 F.3d at 1242.

The remainder of plaintiffs' experts also fail to adequately consider dose response in the context of their Bradford Hill analyses. Drs. Carson, Moorman, Smith-Bindman, Smith and Wolf state that they did not heavily weigh whether there is a dose response in assessing causation.[164] These experts generally state that their causation conclusions rest more heavily on other factors – particularly strength of association, consistency of association and biological plausibility.[165] But those factors do not support a causal inference. As explained throughout this memorandum, there is an objectively weak association in some case-control studies, the remaining studies are facially inconsistent and the other Bradford Hill factors are not close to satisfied (as set forth below). Thus, these witnesses' suggestion that a dose response is less relevant due to other considerations being satisfied is simply pulled from whole cloth and not supported by the science.

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164 (*See* Carson Rep. at 10; Moorman Rep. at 31; Smith-Bindman Rep. at 40; *see also* Smith Rep. at 21; Wolf. Rep. at 15.)

165 (*See, e.g.*, Carson Rep. at 8-11; Smith Rep. at 19-20.)

Finally, several of plaintiffs' experts attempt to speculate as to why the talc studies have not shown clear evidence of a dose response.[166] But these arguments only further underscore the unreliability of their opinions.

***First***, there is no merit to plaintiffs' experts' contention that studies finding no dose-response should be disregarded because they do not measure the frequency and duration of the subjects' talc use (otherwise known as "cumulative use" or "lifetime applications"). For one thing, a number of studies ***have*** measured cumulative use and found ***no dose-response relationship***.[167] For example, Terry 2013 – which Dr. Siemiatycki calls "the most important piece of evidence we have on dose-response"[168] – measured cumulative use and "observed ***no significant trend*** . . . in risk with increasing number of lifetime applications."[169] Similarly,

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166 (*See, e.g.*, Kane Rep. at 35; McTiernan Rep. at 65-66; Moorman Rep. at 30-31; Singh Rep. at 63-64; Plunkett Rep. at 50.)

167 (*See, e.g.*, Smith Dep. 294:14-18 (conceding this fact).) The cumulative use metric is itself problematic because it amplifies the already significant problem of recall bias by doubling the information that study participants have to recall (i.e., not merely the number of years of use, but also how often they used talc during those years). (*See* Moorman Rep. at 30 ("[T]here is some inherent inaccuracy in the measurement of the exposure, as the participants in most studies were asked to recall their duration and/or frequency of use over many years.").)

168 (Siemiatycki Rep. at 45.)

169 Terry 2013 at 811 (abstract) (emphasis added); *see also, e.g.*, Rosenblatt et al., *Genital Powder Exposure and the Risk of Epithelial Ovarian Cancer*, 25(2) Cancer Causes Control 737, 739-40 tbl. 2 (2011) ("Rosenblatt 2011") (attached as Ex. A125 to Tersigni Cert.) ("We noted no evidence that risk of ovarian cancer

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although some of plaintiffs' experts claim that Cramer 2016 provides supportive evidence of a dose-response relationship,[170] "[t]here was no clear pattern suggesting a dose-response effect" in that study; to the contrary, there was a random sine wave pattern with increasing risk, then decreasing risk, then increasing risk with total genital talc applications."[171] And although the cohort

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increased in association with increasing extent of the use of perineal dusting powder (assessed as . . . lifetime number of applications)."); Mills et al., *Perineal talc exposure and epithelial ovarian cancer risk in the Central Valley of California*, 112(3) Int'l J. Cancer 458, 460, 463 (2004) ("Mills 2004") (attached as Ex. A94 to Tersigni Cert.) ("As in other studies, the present study did not find a clear dose response based on duration of use or cumulative use."). Several additional witnesses similarly cite to studies that did not observe a dose response as evidence of a dose response. (*See, e.g.*, Kane Rep. at 35 (opining that "most" studies assessing cumulative use "have found an increased risk of ovarian cancer with increased exposure," when four of the seven cited studies did not); Moorman Rep. at 31 (citing Terry 2013 and Mills 2004); Plunkett Rep. at 50 (asserting that "[t]here are several human studies that provide evidence of a dose-response relationship," even though three of six cited studies did not observe one).) This Court has recognized that citing studies that do not support experts' conclusions is unreliable. *See, e.g.*, *Schepise v. Saturn Corp.*, No. CIV.A. 94-385(MLP), 1997 WL 897676, at *17 (D.N.J. July 30, 1997) (Wolfson, J.).

[170] (*See, e.g.*, Clarke-Pearson Rep. at 6; Wolf Rep. at 7; McTiernan Rep. at 32.)

[171] (Merlo Rep. at 24, 32.) *See also* Cramer et al., *The Association Between Talc Use and Ovarian Cancer: A Retrospective Case-Control Study in Two US States*, 27(3) Epidemiology 334, 336-37 tbl. 1 (2016) (attached as Ex. A25 to Tersigni Cert.) (reporting 1-5 years of daily use being significant, > 5-20 years of daily use being not significant and > 20 years of daily use being significant). (Clarke-Pearson Dep. 192:12-14 (admitting "[t]here is not a consistent dose response" in Cramer 2016); Saenz Rep. at 10, 26-27 (explaining that the Cramer 2016 dose-response "data was sinusoidal").)

studies did not specifically measure cumulative use, each included data on frequency or duration of talc use and found no evidence whatsoever of a dose response.[172] Accordingly, plaintiffs' experts' "cumulative use" argument is not supported by the data and is unreliable.[173]

***Second***, several plaintiffs' experts improperly rely on dose-response calculations that include ***non-exposed*** individuals (i.e., individuals with no reported talc use) as one of the exposure groups in the analysis.[174] This approach

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[172] (Saenz Rep. at 15-16.)

[173] Although plaintiffs' experts maintain that Penninkilampi 2018 likewise shows a dose response by comparing women with more and fewer than 3,600 cumulative applications (*see, e.g.*, Smith-Bindman Rep. at 40; Clarke-Pearson Rep. at 9), their reliance on this study is again misplaced. For one thing, the modest trend observed between the two groups was not statistically significant, since the confidence intervals for the two groups overlapped. (*See* Singh Rep. at 65 (acknowledging those results had "overlapping confidence intervals").) Moreover, the "dichotomous categorization of lifetime use" was arbitrary, "undercut[ting] the significance of this finding." (*See* Diette Rep. at 29.)

[174] Specifically, a significant dose trend is reported in the data from the Terry 2013 study only when nonusers are included in the comparison, and, as noted above, the Terry authors themselves concluded that their overall data reflect "no significant" dose trend. *See* Terry 2013 at 817 ("Taken together, these observations suggest that the significant trend test largely reflects the comparison of ever-regular use with never use."). Nevertheless, Dr. Siemiatycki and others heavily rely on this study to support the existence of a dose response. (*See, e.g.*, Siemiatycki Rep. at 43-44 (arguing that the data from Terry 2013 are "compatible with the presence of an underlying dose-response relationship" and that the Terry study is "the most important piece of evidence we have on dose-response"); McTiernan Rep. at 54 (stating that a "clear dose-response trend was evident" in Terry 2013 when "[c]ompar[ing] . . . never users of genital powder" to various use categories); Clark-Pearson Rep. at 9; Kane Rep. at 35; Smith-Bindman Rep. at 40; *(cont'd)*

creates a risk of false positives because, to the extent the study has reported an association between exposure and risk, that same association could be the driver behind a positive dose-response calculation. The true test of a dose-response relationship is whether there is a difference in incidence between modest and high exposures – and there is no reason to include non-exposed individuals in that analysis. Dr. Siemiatycki agreed with this principle as recently as 2016, when he wrote in a report for a different talc case that "the appropriate statistical test for [dose] trend is one that ***excludes*** the baseline unexposed category (since the baseline category is used for the overall binary RR estimate, and it is preferable to keep the trend test independent of the test for overall RR)."[175] This opinion is

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Smith Rep. at 20 (all relying on Terry 2013).) This amounts to second-level cherry picking, since plaintiffs' experts have both singled out that study to support their opinions and focused on a cherry-picked subset of data within it to reach a conclusion at odds with the conclusion of the article itself. Similarly, as Dr. Ballman explains, three other studies relied on by plaintiffs' experts (Wu 2009, Cramer 2016 and Schildkraut 2016) "include women with no perineal/genital talcum powder exposure" when reporting on dose trends, "which means [such trends] may only be significant because of the observed association between ever use and never use of perineal/genital talcum powder, rather than a true dose-response relationship." (Ballman Rep. at 29.)

[175] (Expert Report of Jack Siemiatycki M.Sc., Ph.D. on Talc Use and Ovarian Cancer at 35-36 (Oct. 4, 2016) (submitted in *Lloyd v. Johnson & Johnson (Plaintiff Eva Echeverria only)*, No. BC628228 (JCCP No. 4872) (Cal. Super Ct.)) (attached as Ex. E13 to Tersigni Cert.) (emphasis added); *see also* Dep. of Jack Siemiatycki, Ph.D. 334:17-345:6, 347:18-348:16, *Oules v. Johnson & Johnson*, No. 2014 CA 088327 B (D.C. Super. Ct. Dec. 16, 2016) (attached as Ex. E1 to Tersigni Cert.)

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absent from his MDL report, and his "sudden reversal of opinion . . . seriously undermines the reliability of" his methodology. *Fireman's Fund Ins. Co. v. Canon U.S.A., Inc.*, 394 F.3d 1054, 1059 (8th Cir. 2005).

***Third***, plaintiffs' experts suggest that the lack of precise data regarding the quantity of talcum powder used by study participants somehow obviates the need to establish a dose-response.[176] While plaintiffs are correct that the data are imprecise (indeed, this a significant limitation of all the relevant studies),[177] the burden to prove causation does not diminish when an element of proof is difficult

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(explaining he "favor[s] excluding the nonusers" because "the trend test should be kept separate from the ever never result").) Dr. Siemiatycki now opines that it is sometimes appropriate to include nonusers in the analysis, specifically when a study does not separately report on whether there is an association between any talc use and no talc use. (Siemiatycki Rep. at 43.) Even if this view were correct or supported by anything other than his *ipse dixit*, the Terry study would not satisfy his condition, since it reported on both ever/never use and dose trends. *See* Terry 2013 at 817 tbl. 4.

[176] (*See, e.g.*, Singh Rep. at 55 ("Ascertaining *dose response* relationship with talc and ovarian cancer is difficult because of the challenges in quantifying talcum powder use usually collected by self-reported data . . . ."); Clarke-Pearson Rep. at 9 (similar); Kane Rep. at 34-35 (similar); McTiernan Dep. 53:18-22 (similar).)

[177] (*See* Diette Rep. at 30-31 (recognizing that "it is impossible from the studies to determine how much, if any, talcum powder was applied to the perineum, and likewise impossible to measure how much, if any, talcum powder migrated into the vagina, across the cervix, up through the uterus and eventually reached the ovaries," but further noting that "these same issues of validity of the exposure measure are just as important for assessing the overall proposition of whether or not talcum powder causes ovarian cancer" as they are for assessing dose response).)

to study. *See, e.g.*, *Guinn v. AstraZeneca Pharm. LP*, 602 F.3d 1245, 1250, 1255 (11th Cir. 2010) (per curiam) (expert was "still required to" conduct a differential diagnosis to eliminate alternative causes for her opinion to be reliable, even though she testified that "there was no scientific way to" do so); *Perry*, 564 F. Supp. 2d at 467-68 ("[M]ak[ing] clear that the non-existence of good data does not allow expert witnesses to speculate or base their conclusions on inadequate supporting science").

***Finally***, several of plaintiffs' experts hypothesize that the dose response for talc and ovarian cancer may not be "monotonic" or "linear," but rather may be a "threshold" response – i.e., a risk that uniformly increases after a certain minimal level of exposure.[178] But this is pure speculation; as Dr. Siemiatycki explains, "[m]ost commonly . . . the relationship between exposure and risk is monotonic; that is, as one increases, so does the other."[179] And, in any event, if there really were a threshold effect, studies would reflect a consistently increased risk over a

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[178] (*See, e.g.*, Moorman Rep. at 31 (one "possible reason[] why not all studies observed dose-response relationships" is because "the dose-response relationship may not be a simple linear trend"); Wolf Rep. at 15 (similar); Clarke-Pearson Rep. at 9 ("asbestos exposure and mesothelioma is generally thought to have a 'threshold response'").)

[179] (Siemiatycki Rep. at 15.)

certain threshold; yet, the studies report highly inconsistent risks,[180] and plaintiffs' experts are unable to estimate what the putative threshold is.[181] Courts recognize that experts who "offer[] no testimony about the dose of [the chemical] required to [cause] injur[y]" have not undertaken a reliable causation methodology. *See, e.g.*, *McClain*, 401 F.3d at 1241; *In re Lipitor (Atorvastatin Calcium) Mktg., Sales Practices & Prods. Liab. Litig.*, 174 F. Supp. 3d 911, 933, 935 (D.S.C. 2016) (excluding expert opinion where there was no "meaningful or reliable analysis[] of whether particular dosages are capable of causing [the disease]"); *Watson v. Dillon Co.*, 797 F. Supp. 2d 1138, 1154 (D. Colo. 2011) (finding the expert's "opinion . . . [wa]s not based on a reliable foundation" where "there [wa]s little to no reliable evidence establishing a threshold dose").

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[180] *See, e.g.*, Mills 2004 at 460 (reporting risks of 1.03, 1.81, 1.74 and 1.06 for ascending quartiles); Cook 1997 at 463 (reporting risks of 1.8, 1.6, 1.2 and 1.8 across four categories of "cumulative lifetime days"); Rosenblatt 2011 at 740 (reporting risks of 1.21, 2.08, 0.87 and 0.87 across four categories of increasing lifetime applications ).

[181] To the extent Dr. McTiernan speculates that ***any*** dose of talc can increase the risk of ovarian cancer (*see* McTiernan Dep. 54:5-56:19), this would be a radical view that is even less supported than the "'any exposure' to asbestos" theory that courts have resoundingly rejected, *see, e.g.*, *Anderson v. Ford Motor Co.*, 950 F. Supp. 2d 1217, 1223-24 (D. Utah 2013) (rejecting the "every exposure" theory as "based on [a] lack of information sufficient to show the level of exposure which does not create a risk"); *McMunn v. Babcock & Wilcox Power Generation Grp., Inc.*, 869 F.3d 246, 271 (3d Cir. 2017) (expert opinion that any exposure to radiation causes disease is insufficient to create genuine issue of fact), *cert. denied*, 138 S. Ct. 1012 (2018).

Because plaintiffs' experts have failed to demonstrate the existence of a dose response, their causation analyses are all the more unreliable and should be excluded under *Daubert.*

**D. The Other Bradford Hill Factors Do Not Support Causation.**

Plaintiffs' experts' opinions regarding the remaining Bradford Hill factors – biological plausibility, specificity, coherence, analogy, experiment and temporality – also do not reliably support a causal inference.[182] As Dr. Merlo testified, the Court need not even consider these factors because causation cannot be established when an association is weak, the studies are inconsistent, and there is no evidence of dose response.[183] But even if it were necessary to assess these factors, they only further highlight the unreliability of plaintiffs' experts' causation analyses, as discussed further below.

***Biological Plausibility*.** Plaintiffs' expert's opinions regarding biological plausibility are unreliable and inadmissible for all the reasons set forth in

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[182] The consideration of alternative explanations – which some consider an additional factor in the Bradford Hill analysis – also does not support drawing a causal inference because, as explained in Section I.A, *supra*, plaintiffs' experts have failed to rule out that confounding variables or recall bias may account for the small association reported in a subset of the literature.

[183] (*See* Merlo Dep. 178:24-179:5 ("[W]ith a lack of strength of association, with a lack of consistency between studies and with a lack of dose response, biologic plausibility doesn't matter because there's no causal association between talcum powder and ovarian cancer based on the medical literature.").)

defendants' Biological Plausibility Brief, incorporated herein. Simply put, and as the Penninkilampi meta-analysis notes, "the evidence remains insufficient to understand the mechanisms [by which talc purportedly causes ovarian cancer] with any reasonable certainty."[184]

Presumably because their biological evidence is so weak, some of plaintiffs' experts have taken the position that biological plausibility is not a required part of the causation analysis, relying on statements by Bradford Hill, in a 1965 address, that the biological plausibility factor of his famed causation analysis was "a feature I am convinced we cannot demand" in every case.[185] That statement, however, was made in the context of defending the Bradford Hill method against critiques that it would not allow for a finding of causation in circumstances where there was an overwhelming statistical association between an agent and disease, and science had not yet conclusively proven the precise method by which the disease occurred. By way of example, the speech referenced the "*enormous* increase of scrotal cancer in the chimney sweeps" in the late-18th century and early-19th century, the mortality rate of whom was "***some 200 times that of workers who were not***

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184 Penninkilampi 2018 at 45.

185 Hill 1965 at 298. (*See also, e.g.*, Siemiatycki Rep. at 52-53; Moorman Rep. at 32-33; *but see* Clarke-Pearson Rep. at 9 (biological plausibility "is obviously a critical factor when forming opinions on causation").)

***specially exposed to tar or mineral oils***."[186] Hill stated that the fact that there was "no biological knowledge to support (or to refute)" the observation of such a strong association between tar/oil exposures and scrotal cancer in the 18th century did not mean that the association should have been "dismiss[ed]" out of hand by science. *Id*. at 298. In so concluding, Hill expressly noted that "[w]hat is biologically plausible depends upon the biological knowledge of the day." *Id*.

The "knowledge of the day" is different now than it was in the 18th century. It is no longer true that there is "no biological knowledge" of what causes cancer. To the contrary, it is well established that cancer results from genetic cellular changes, and plaintiffs lack any evidence that talc is mutagenic. Nor do plaintiffs have any evidence of an overwhelming association between perineal talc use and ovarian cancer that would allow causation to be presumed absent a cogent biological mechanism by which it occurs. Rather, as discussed extensively above, the risk ratios at issue are, at most, weak, and in the cohort studies, non-existent. In these circumstances, it is all the more essential that plaintiffs be able to demonstrate the biological plausibility of their causation theory.[187]

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186 Hill 1965 at 295 (second emphasis added).

187 *See, e.g.*, Wynder 1982 at 465 ("Because chance or bias can easily produce a spurious weak association, ***the need to seek supporting evidence is greater with weak than with strong associations***.") (emphasis added); *Mirena*, 341 F. Supp. 3d at 286 (holding that where "scholarship has *not* shown more than a correlation,

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This was a significant consideration in the *Carl* ruling. There, Judge Johnson concluded that the plaintiffs' experts had conducted a "narrow and shallow examination of the science" to support their causal opinions, emphasizing their "failure to provide a coherent explanation to support their hypothesis for biologic plausibility." 2016 WL 4580145, at *12. In excluding their causation opinions, Judge Johnson also observed that their failure to address talc's lack of mutagenicity was a crucial flaw; that they could not reliably articulate "what it is about talc in the ovaries . . . that sets off a chain of events which purportedly causes ovarian cancer"; and that merely "[u]ttering the term inflammation does not explain the etiology of ovarian cancer." *Id.* at *14, *21.

Although a number of plaintiffs' experts point to the alleged presence of asbestos and other alleged harmful constituents in talc as supporting a plausible biological mechanism[188] (in an apparent attempt to overcome Judge Johnson's ruling), this theory is unavailing because, as plaintiffs' experts concede, the effect of alleged asbestos contamination would be reflected in the epidemiological

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subject to identifiable confounders, between [the product and the disease]," "it is ***not enough***" "for an expert as to general causation to opine that a biological pathway exists but is not well understood") (second emphasis added); Epidemiology Reference Manual at 602 (explaining that "epidemiologist[s] will scrutinize [weak] associations more closely").

188 (*See, e.g.*, McTiernan Rep. at 56; Smith Rep. at 19; Singh Rep. at 19.)

studies on talc.[189] As Dr. Diette explains, "if talc products have generally contained asbestos, the epidemiological literature would reflect the risks of asbestos in talc."[190] In any event, plaintiffs' experts' opinions regarding asbestos and other allegedly harmful constituents are unreliable and inadmissible as fully explained in Defendants' Memorandum of Law in Support of Motion to Exclude Plaintiffs' Experts' Opinions Related to Asbestos.

***Specificity Of Association.*** Plaintiffs' experts generally place minimal weight on the specificity factor, which considers whether the exposure at issue has been associated with a specific disease.[191] In truth, the proposed association in this litigation is highly ***unspecific***, because most of plaintiffs' experts take the position

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189 (*See, e.g.*, Moorman Dep. 124:20-126:6 (stating that her opinion is "based on talcum powder products, whatever is contained them -- in them" and that the alleged presence of asbestos "doesn't change the . . . epidemiologic studies"); Singh Dep. 273:6-9 (similar); Dep. of Michael Birrer, M.D., Ph.D. 57:11-58:2, Mar. 29, 2019 (attached as Ex. B36 to Tersigni Cert.) (explaining that any effect of asbestos "would have been obvious from the [talc] data and it's not").)

190 (Diette Rep. at 3, 6.)

191 (*See, e.g.*, Kane Rep. at 34; Siemiatycki Rep. at 66; Smith-Bindman Rep. at 39; Singh Rep. at 63-64 ("I placed less weight on absolute specificity of the association between talcum powder exposure and ovarian cancer given the multi-causal nature of the outcome . . . .").) Defendants do not dispute that the specificity factor is considered by many to be less important today than it was when first proposed by Bradford Hill. That does not mean, however, that it should be wholly disregarded, especially where, as here, it clearly weighs against a causal inference.

that talc use causes every subtype of epithelial ovarian cancer, even though these are effectively different diseases.

As Dr. Smith-Bindman explains, the subtypes of ovarian cancer "vary in their pathological appearance, molecular biology, risk factors, etiology, and prognosis."[192] The different subtypes also arise from different tissues – for example HGSOC, largely arises from the fallopian tubes, while endometrioid and clear cell carcinoma develop in the uterine endometrium – and they develop as a result of different sets of genetic mutations. Unsurprisingly, then, the different subtypes of ovarian cancer all have different risk factors,[193] and it is unlikely that one substance could cause all (or even most) of them.[194] This lack of specificity further highlights the unreliable nature of plaintiffs' experts' opinions. *See Zoloft I*, 26 F. Supp. 3d at 463 (excluding expert's testimony on causation because, although the expert cited studies demonstrating that "Zoloft [wa]s significantly

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[192] (Smith-Bindman Rep. at 9.) The remainder of plaintiffs' experts generally gloss over the differences between the ovarian cancer subtypes. As set forth in defendants' Biological Plausibility Brief, those differences have important implications for plaintiffs' experts' biological plausibility theories, and their failure to account for them underscores the unreliability and superficiality of their analyses.

[193] (*See* Neel Rep. at 13-14.)

[194] (*Cf.*, *e.g.*, Dep. of Michael Crowley, Ph.D. 212:14-213:2, Jan. 4, 2019 (attached as Ex. B37 to Tersigni Cert.) (agreeing that is possible that an agent can cause one type of cancer but not another).)

associated with septal defects in the heart," the expert's "opinion [wa]s not limited to [that] one injury").

***Coherence.*** Coherence means that "the cause-and-effect interpretation of our data should not seriously conflict with the generally known facts of the natural history and biology of the disease."[195] In other words, there should be "coherence across all the available data, e.g., cell line, animal and human data."[196] The theory that talc use causes ovarian cancer is not coherent with existing scientific knowledge, and plaintiffs' experts' contrary conclusions are unreliable.[197]

Plaintiffs' experts are able to conclude that the coherence factor favors causation only by ignoring numerous contradictions in the available data.[198] As

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195 Hill 1965 at 298.

196 (Ballman Rep. at 20.)

197 Of note, several of plaintiffs' experts give the coherence factor "considerable weight" (*e.g.*, Moorman Rep. at 37-38; Singh Rep. at 65-66; Kane Rep. at 36), while others discount it (*e.g.*, Siemiatycki Rep. at 67 (giving coherence "[not] much weight in this context"); McTiernan Rep. at 29, 67 (stating that "it would be difficult to determine" whether coherence is satisfied and that she does not weigh this factor as heavily as others)).

198 (*See* Carson Rep. at 10 (discussing several "factors related to ovarian cancer" but ignoring the issues discussed in the text); Kane Rep. at 36 (arguing that coherence is satisfied simply because consistency of association and biological plausibility are purportedly satisfied); Clarke-Pearson Rep. at 9; Wolf Rep. at 16 (both arguing coherence is satisfied because "[t]he findings and conclusions from epidemiological, animal, and in vitro studies are coherent with what is known about ovarian cancer," and because "[t]here is also consistency with what is known about other" types of cancer); Moorman Rep. at 38; McTiernan Rep. at 67; Singh *(cont'd)*

courts have held, this type of methodology – selectively addressing certain data and failing to explain contradictory evidence – renders their opinions unreliable. *Zoloft I*, 26 F. Supp. 3d 460-62 (excluding expert for "selectively discuss[ing]" the data "and fail[ing] to account adequately for contrary evidence"); *In re Bextra & Celebrex Mktg. Sales Practices & Prod. Liab. Litig.*, 524 F. Supp. 2d 1166, 1176 (N.D. Cal. 2007) (an expert may not ignore "evidence that contradicts his conclusion").

For one thing, as just noted, there are numerous subtypes of ovarian cancer, and the notion that talc use would cause all of them is incoherent.[199] Plaintiffs' theories are also incoherent because the one thing that all ovarian cancers have in common is that they arise as a result of genetic mutations,[200] and there are no data

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Rep. at 65-66; Smith-Bindman Rep. at 41 (all essentially arguing that coherence is satisfied because biological plausibility is purportedly satisfied); *see also* Siemiatycki Rep. at 64-67 (appearing to consider coherence as part of biological plausibility analysis, but later separately stating that coherence cannot be evaluated under Hill's rubric).)

[199] (Neel Rep. at 28 ("Nor does it make logical sense that talc use would cause multiple subtypes of ovarian cancer, which have different cells of origin, different types of mutations and mutational effects, and therefore likely different oncogenic mechanisms.").)

[200] (*See, e.g.*, Clarke-Pearson Rep. at 3 ("By definition, cancer results from gene mutations . . . ."); Neel Rep. at 5 ("Cancer . . . is a disease of the genome, caused by 'mutations' . . . .").) *See also Carl*, 2016 WL 4580145, at *14 (it is "universally accepted that mutations in critical genes is the mechanism that causes cancer").

to suggest that talc causes genetic mutations.[201] As IARC put it, "[t]he limited number of studies available on the genetic toxicity of talc *in vitro* gave negative results."[202]

Plaintiffs' experts' theories are also incoherent because there are ***no*** animal studies showing that talc use causes ovarian cancer (or any type of cancer). Indeed, researchers have repeatedly attempted to induce ovarian cancer in laboratory animals with extremely high doses of talc and have failed to do so.[203] Most notably, a 2009 study treated rats with intravaginal and perineal talc and observed no neoplastic change (i.e., no cancer), and a 1984 study injected talc directly into the rat ovarian bursa and similarly observed no malignancies.[204] The fact that the

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201 Although plaintiffs' expert Dr. Saed claims to be the first to have induced genetic mutations in cells treated with talc, his work was highly unscientific and potentially fraudulent for all the reasons set forth in defendants' motion to exclude his opinions.

202 IARC 2010 Monograph at 411.

203 *See id.* at 410 (summarizing results of animal studies, observing that only one study (NTP 1993) observed lung tumors, and only in a subset of rats). (*See also* Expert Report of Kelly Tuttle, Ph.D., C.I.H. at 17-18, Feb. 25, 2019 (attached as Ex. C26 to Tersigni Cert.) (summarizing studies; explaining that NTP 1993 has been criticized and interpreted as not having shown tumor development from talc, since the strain of rats at issue are prone to the observed tumors).)

204 Keskin et al., *Does Long-Term Talc Exposure Have a Carcinogenic Effect on the Female Genital System of Rats? An experimental pilot study*, 280 Archives Gynecol. Obstet. 925 (2009) (attached as Ex. A85 to Tersigni Cert.); Hamilton et al., *Effects of Talc on the Rat Ovary*, 65(1) Br. J. Exp. Pathol. 101, 106 (1984) (attached as Ex. A53 to Tersigni Cert.).

talc-ovarian cancer theory has not been proven by the very scientific experiments that have attempted to test it further highlights the incoherence of plaintiffs' theory.

Plaintiffs' experts also fail to reconcile their opinions with studies that have investigated use of talcum powder on diaphragms and condoms and have found no increased risk.[205] It is illogical and incoherent to opine that talc applied to the ***outside*** of the genital tract (i.e., on the perineum or near the perineum on underwear or sanitary napkins) can cause ovarian cancer, when the only evidence on point suggests that there is no association when talc is placed ***directly into*** the genital tract.[206] And the fact that high doses of talc are administered safely in pleurodesis[207] – and that workers exposed occupationally to talc have not been

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[205] *See, e.g.*, Penninkilampi 2018 at 42, 44 ("Talc use on diaphragms or on sanitary napkins was not individually associated with increased risk of ovarian cancer."); Fiume 2015 at 122S (similar). While Dr. Singh attempts to dismiss these studies as supposedly "obsolete," he does not identify any scientific source that agrees with this position or any evidence showing that talc use on condoms and diaphragms is associated with an increased risk. (*See* Singh Rep. at 16-17, 26-27.)

[206] (Diette Rep. at 25 ("Studies pertaining to use of talcum powder on diaphragms and condoms have shown a consistent lack of risk."); Holcomb Rep. at 17 ("[S]ome analyses limited to modes of exposure that ensure internal deposition of the talc particles, like dusting of diaphragms or condoms show no increased risk of ovarian cancer with these behaviors.") (footnotes omitted).)

[207] (Holcomb Rep. at 18-19; Neel Rep. at 28 ("[H]umans given high doses of talc in other body cavities (e.g., via pleurodesis) or exposed occupationally do not have increased cancer risk.").)

shown to be at an increased risk of developing cancer[208] – only adds to the incoherence of plaintiffs' experts' opinions.

A final indication of incoherence is the lack of any increased risk of cancer in tissues that are much closer to the perineum than the fallopian tubes and ovaries. If talc were carcinogenic, it would likely cause vaginal, cervical and endometrial cancer, since those tissues are closer to the perineum and thus likely to be first exposed if talc enters the vaginal cavity.[209] But it does not, as plaintiffs' experts concede.[210] This, too, shows that plaintiffs' experts' causation theory is not coherent with existing scientific knowledge.[211]

***Analogy.*** Plaintiffs' experts generally opine that the putative causal relationship between talc and ovarian cancer can be analogized to asbestos causing

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208 (Neel Rep. at 28.)

209 (*See* Smith Dep. 347:14-18 (agreeing that if talc migrates to the ovaries, tissues and organs along the genital tract would be exposed to talc).)

210 (*See, e.g.*, Smith Dep. 375:1-24 (testifying that she is not aware of any evidence that genital talc use increases the risk of vulvar, vaginal, uterine or rectal cancer); Carson Dep. 200:9-14 (no studies that show inflammation or oxidative stress as a result of genital talc use in the rectal, vulvar, vaginal, cervical and uterine tissues); Clarke-Pearson Dep. 213:22-25 (same).)

211 The incoherence of plaintiffs' experts' opinions is further underscored by the fact that anti-inflammatories have not been shown to reduce the risk of ovarian cancer, as discussed more fully in defendants' Biological Plausibility Brief.

ovarian cancer, mesothelioma or lung cancer.[212] As explained below, these opinions are scientifically unsubstantiated and unreliable.

As an initial matter, plaintiffs' experts are wrong that there is reliable evidence indicating that asbestos causes ovarian cancer. As set forth in defendants' briefing that addresses plaintiffs' experts' asbestos opinions, there are no data suggesting that exposure to asbestos at non-occupational levels is associated with ovarian cancer.[213] And the occupational studies that do exist primarily examine exposure to crocidolite asbestos – a type of asbestos fiber that is not alleged to be a contaminant of talc.[214]

In any event, the proposed asbestos analogy is unreliable for other reasons as well. For starters, asbestos and talc are distinct minerals with distinct chemical structures and morphology, and talc lacks the unique chemical and physical properties that make asbestos harmful – i.e., a fibrous shape, flexibility and

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212 (*E.g.*, Clarke-Pearson Rep. at 9; Kane Rep. at 13-14; Smith-Bindman Rep. at 41.) This factor, too, does not appear to weigh heavily in plaintiffs' experts' causation opinions. For example, Dr. Siemiatycki tepidly states that "there is an argument for an analogy between talc and asbestos" (Siemiatycki Rep. at 67) and Dr. Smith similarly "would suggest the analogy of asbestos causing ovarian cancer and mesothelioma" (Smith Rep. at 21). These "argu[able]" and "suggest[ed]" analogies reek of speculation and are not scientific evidence of causation.

213 (*See* Defs.' Mem. in Supp. of Mot. To Exclude Pls.' Experts' Asbestos-Related Opinions at 83-87.)

214 (*See id.* at 89.)

durability.[215] For example, unlike amphibole asbestos, which can remain in the body for decades, talc has a "maximum residence time" of approximately eight years.[216] Likewise, in contrast to asbestos, "talc particles are normally plate-like" and only rarely fibrous.[217] These and other characteristics are critical components that allow asbestos to evade a body's defense mechanisms and initiate disease causation.[218] Plaintiffs' experts' conclusory opinions regarding the analogy factor fail to address these fundamental distinctions, or even to suggest what particular qualities of asbestos that make it dangerous are ostensibly shared by talc. These

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[215] (*See* Mossman Rep. at 16-17, 23.) *See also Glastetter v. Novartis Pharm. Corp.*, 252 F.3d 986, 990 (8th Cir. 2001) (per curiam) ("Even minor deviations in molecular structure can radically change a particular substance's properties and propensities."); *McClain*, 401 F.3d at 1246 (agreeing that "even small differences in chemical structure can sometimes make very large differences in the type of toxic response that is produced") (citation omitted).

[216] *See* IARC 2010 Monograph at 281.

[217] Int'l Agency for Research on Cancer, World Health Org., 100C *Monographs on the Evaluation of Carcinogenic Risks to Humans: Arsenic, Metals, Fibres, and Dust* 230 (2012) ("IARC 2012 Monograph") (attached as Ex. A70 to Tersigni Cert.). (*Contra* Kane Rep. at 13 (noting only that talc and asbestos are "somewhat morphologically distinct").)

[218] *See, e.g.*, IARC 2012 Monograph at 283-290 (explaining that the "pathogenic potential" of asbestos depends on its crystal structure, aspect ratio, fiber size, surface reactivity and biopersistence, among other factors); *see also* Gualtieri, *Towards a quantitative model to predict the toxicity/pathogenicity potential of mineral fibers*, 361 Toxicol. & Applied Pharmacol., 89 (2018) (attached as Ex. A52 to Tersigni Cert.) (explaining that the chemistry, molecular arrangement, size, biodurability and surface reactivity of a mineral could affect its toxicity and carcinogenic potential).

failures render their "analogy" opinions unreliable and inadmissible. *See McClain*, 401 F.3d at 1246 (reversing admission of expert who "failed to show that the PPA analogy is valid or that the differences in chemical structure between PPA and ephedrine make no difference").

Plaintiffs' experts' opinions analogizing talc to asbestos are unreliable for the additional reason that they cannot be reconciled with the available data regarding talc use and mesothelioma. If talc and asbestos were sufficiently similar to support a reliable analogy, it would be expected that individuals who inhale talc would develop mesothelioma, a disease known to be caused by asbestos. But plaintiffs' experts have not pointed to ***any*** evidence showing that talc use increases the risk of mesothelioma. *See McClain*, 401 F.3d at 1245-46 (reversing admission of expert who did not support proposed analogy with "any scientific evidence"). Indeed, studies examining the incidence of diseases in talc miners and millers – who regularly inhale far more talc than perineal users – have not shown any association between talc and mesothelioma.[219]

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[219] *See, e.g.*, Coggiola et al., *An Update of a Mortality Study of Talc Miners and Millers in Italy*, 44(1) Am J Ind Med. 63 (2003) (attached as Ex. A20 to Tersigni Cert.); Wild et al., *A Cohort Mortality and Nested Case-Control Study of French and Austrian Talc Workers*, 59(2) Occup Environ Med. 98 (2002) (attached as Ex. A152 to Tersigni Cert.); Wergeland et al., *Morbidity and Mortality in Talc-Exposed Workers*, 17(4) Am J Ind Med. 505 (1990) (attached as Ex. A151 to Tersigni Cert.).

Finally, although Dr. Kane claims that the association between asbestos exposure and mesothelioma is analogous to talc exposure and ovarian cancer, this comparison falls short because mesothelioma and ovarian cancer are very different diseases. For example, Dr. Kane opines that epithelial ovarian cancer "has striking morphological similarities to mesothelioma"[220] but generally supports this opinion only with misleading high-magnification photographs that obscure the diseases' differences.[221] In fact, mesothelioma and ovarian cancer have significantly different morphologies, etiologies and pathological markers.[222]

For all of these reasons, plaintiffs' experts have "use[d] . . . an unreliable analogy," and their opinion that the analogy factor supports causation is scientifically unsupported. *See McClain*, 401 F.3d at 1247.

***Experiment.*** This consideration likewise provides no reliable support for plaintiffs' experts' causation opinions. Plaintiffs' experts agree that randomized clinical trials – the primary type of experimental evidence – have not been

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220 (Kane Rep. at 14.)

221 (Expert Report of Robert J. Kurman, M.D. at 14, Feb. 25, 2019 (attached as Ex. C37 to Tersigni Cert.))

222 (*See id.* at 14-15 (explaining, for example, that the chemical calretinin is a marker for mesothelioma, but not HGSOC).)

conducted on talc and ovarian cancer,[223] or they ignore the "experiment" consideration altogether.[224] To the extent plaintiffs' experts argue that there is "compelling" experimental evidence supporting causation (i.e., animal and in vitro studies),[225] they are wrong for all the reasons set forth in defendants' Biological Plausibility Brief. Indeed, as noted above, animal studies have shown that even huge doses of talc do not cause ovarian cancer.

***Temporality.*** A number of plaintiffs' experts place outsized importance on the observed temporal association between talc use and ovarian cancer.[226] But the notion that talc use precedes the onset of ovarian cancer is unremarkable given that ovarian cancer typically develops late in life, whereas most women begin using talc by their mid-20s.[227] For this reason, Dr. Moorman's position that the absence

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[223] (*E.g.*, McTiernan Rep. at 29; Singh Rep. at 66.) Perhaps for this reason, plaintiffs' experts generally seek to minimize this factor. (*E.g.*, Singh Rep. at 66 (experiment "weighted as less important").)

[224] (*See* Siemiatycki Rep. at 62-67.)

[225] (Smith-Bindman Rep. at 41; *see also, e.g.*, Smith Rep. at 21; Kane Rep. at 36-37.)

[226] (*E.g.*, McTiernan Rep. at 65 (placing "great weight" on this "important component in the causal analysis"); Smith-Bindman Rep. at 39; Kane Rep. at 34 ("important factor in my analysis"); Singh Rep. at 64 ("significant weight").)

[227] (*See, e.g.*, Wolf Dep. 320:16-321:1 (agreeing that 80% of talc users start by age 25).) It is notable that a temporal association is most likely to be shown by cohort studies, which, as plaintiffs' experts explain, obtained exposure data "before any women were diagnosed with ovarian cancer." (Kane Rep. at 34; *see also* Singh Rep. at 10 (cohort studies "establish[] temporality wherein the exposure

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of temporality "would be fatal to a causal inference, [but] its presence is not particularly compelling support for causation"[228] is correct, and the other witnesses' opinions to the contrary lack a scientific basis. *See Guinn*, 602 F.3d at 1254 ("Temporal proximity is generally not a reliable indicator of a causal relationship."); *Buzzerd v. Flagship Carwash of Port St. Lucie, Inc.*, 669 F. Supp. 2d 514, 530 (M.D. Pa. 2009) ("[T]emporal connection standing alone is entitled to little weight in determining causation.") (citations omitted), *aff'd*, 397 F. App'x 797 (3d Cir. 2010); *Roche v. Lincoln Prop. Co.*, 278 F. Supp. 2d 744, 764 (E.D. Va. 2003) ("An opinion based primarily, if not solely, on temporal proximity does not meet *Daubert* standards.").

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In sum, plaintiffs' experts' Bradford Hill analyses lack scientific support and ignore substantial contrary science with respect to virtually every factor of the

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precedes the outcome").) *See also* Epidemiology Reference Manual at 558 ("One advantage of the cohort study design is that the temporal relationship between exposure and disease can often be established more readily than in other study designs, especially a case-control design."). Yet, the talc cohort studies have ***not*** observed an association between talc use and ovarian cancer. Moreover, if the latency of ovarian cancer is as long as some of plaintiffs' experts hypothesize (up to 40 years), it cannot be ruled out that ovarian cancer initiates before talc use in some women.

[228] (Moorman Rep. at 29.)

analysis. Because these analyses lack scientific rigor, they should be excluded under *Daubert*.

## II. DR. SMITH-BINDMAN'S META-ANALYSIS FLUNKS *DAUBERT* AND SHOULD BE EXCLUDED.

One of plaintiffs' epidemiologists, Dr. Smith-Bindman, purports to have conducted a "New Systematic Meta-Analytic Review" to further support her conclusion that talc use causes ovarian cancer.[229] Even though the talc literature includes numerous meta-analyses, Dr. Smith-Bindman saw fit to conduct a new "review" to focus on "regular" talc users and women who developed HGSOC.[230] Dr. Smith-Bindman purports to show via her meta-analysis that "regular" talc use is associated with a 50% increase in the risk of developing HGSOC.[231] This conclusion is unsupported, and the methodology used to reach it is unreliable because it was: (1) designed to reach a desired result; (2) based on subjective inclusion and exclusion criteria that were inconsistently applied and not reproducible; and (3) premised on inaccurate data.

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229 (Smith-Bindman Rep. at 30-34.) There is actually no such thing as a "systematic meta-analytic review." Dr. Smith-Bindman technically performed a meta-analysis since she generated quantitative estimates of the associations she studied. (Ballman Rep. at 43.)

230 (Smith-Bindman Rep. at 31.)

231 (*Id.* at 34.)

***First***, Dr. Smith-Bindman conducted a conclusion-driven and scientifically unjustified "post-hoc subgroup analysis" – i.e., she analyzed particular subsets of data from prior cherry-picked studies ***after*** she reviewed the larger body of literature and formulated a thesis.

"[R]esults-oriented, *post-hoc* re-analyses of existing epidemiological studies are disfavored by scientists and often deemed unreliable by courts . . . ." *Zoloft II*, 2015 WL 7776911, at *14. As Dr. Merlo explains, these analyses are unreliable because they "allow[] the researcher to start with a conclusion and work backwards, which is exactly the opposite of the scientific method."[232] And as plaintiffs' expert Dr. Siemiatycki has noted, it is difficult to justify post-hoc subgroup analyses because "the investigators of the original studies . . . chose which would be the 'best' result to represent the study, and this . . . is more reliable than outside authors making that decision."[233]

Post-hoc subgroup analyses are particularly problematic when an expert has "manipulated the data to achieve a desired result," *Snodgrass v. Ford Motor Co.*, No. 96-1814(JBS), 2002 WL 485688, at *12 (D.N.J. Mar. 28, 2002), for example

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[232] (Merlo Rep. at 41.) In other words, "associations discovered in a subgroup analysis" may be large because they were "engineered to maximize that value." (Ballman Rep. at 39 (quoting Stallone, *The use and abuse of subgroup analysis in epidemiological research*, 16(2) Prev. Med. 183 (1990)).)

[233] (Siemiatycki Rep. at 41.)

by "self-select[ing] [a] subset of supportive studies" and excluding others without providing a scientific basis for doing so, *Zoloft I*, 26 F. Supp. 3d at 461-62. As Dr. Siemiatycki additionally put it, "[i]n order to implement a meta-analysis it is necessary to find ***all relevant studies*** on a topic."[234]

For these reasons, courts (including this Court) routinely exclude unreliable post-hoc subgroup analyses. *See, e.g.*, *Bracco*, 627 F. Supp. 2d at 452 (agreeing that expert's post-hoc analysis "violate[d] the rules and underlying rationale for performing scientific analysis in a prospective, unbiased manner and that such testimony based on flawed methodology and flawed assumptions should be excluded") (citation omitted); *Zoloft I*, 26 F. Supp. 3d at 461-62; *Bextra*, 524 F. Supp. 2d at 1176 (excluding testimony where expert "reache[d] his opinion by first identifying his conclusion . . . and then cherry-picking observational studies that support his conclusion and rejecting or ignoring the great weight of the evidence that contradicts his conclusion"). For example, in *Zoloft III*, the Third Circuit affirmed exclusion of an expert who performed a post-hoc subgroup analysis in which he, "without explanation . . . performed a meta-analysis on two studies but not on any of the other studies"; "inexplicably excluded another study" that met his criteria; and "reanalyzed two studies to control for" a certain confounder when

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234 (Siemiatycki Rep. at 16 (emphasis added).)

"[t]he need for [doing so] was unclear." *Zoloft III*, 858 F.3d at 798. The Third Circuit concluded that the expert's approach "seem[ed] conclusion-driven," explaining that the fact that he "applied these techniques inconsistently, without explanation, to different subsets of the body of evidence raises real issues of reliability." *Id.*

Dr. Smith-Bindman took a similarly unreliable approach. She purports to have conducted her review in order to focus on particular subgroups, "regular" talc users and those who developed HGSOC.[235] But prior to forming her hypothesis, Dr. Smith-Bindman had already reviewed the relevant studies and underlying data.[236] And only with that knowledge in hand did Dr. Smith-Bindman choose to focus on "regular use" and HGSOC. Accordingly, her review was the very definition of "conclusion-driven." *Zoloft III*, 858 F.3d at 798.

Moreover, like the expert in *Zoloft III*, Dr. Smith-Bindman did not apply her contrived criteria faithfully. *See also, e.g.*, *Amorgianos v. Nat'l R.R. Passenger Corp.*, 303 F.3d 256, 268-69 (2d Cir. 2002) (affirming exclusion of expert who "failed to apply his own methodology reliably"). In particular, she admitted that

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235 (Smith-Bindman Rep. at 31.)

236 (Dep. of Rebecca Smith-Bindman, M.D., Vol. I ("Smith-Bindman 2/7/19 Dep.") 52:14-21, Feb. 7, 2019 (attached as Ex. B40 to Tersigni Cert.) (testifying that her systematic review "grew out of [her] reading the literature"); *id.* 164:3-9 (agreeing that she "generated the research questions after doing the initial literature review").)

she did not include every study that contained data that fit her definition of "regular" use.[237] Indeed, she originally determined that one study – Rosenblatt 2011, which reported a ***negative*** association for heavy lifetime use of talc – fit her selection criteria but eventually decided to omit it without explanation.[238] Dr. Smith-Bindman later speculated that she omitted the study because it had "no impact" on her results.[239] But her underlying data show that the omission ***increased*** her odds ratio from 1.38 to 1.52 for "regular use" and HGSOC.[240] In other words, Dr. Smith-Bindman ***would not have achieved*** a 1.52 relative risk for HGSOC if she had included Rosenblatt 2011.

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237 (*See* Smith-Bindman 2/7/19 Dep. 175:22-176:21 ("I do not know why [Cramer 1999] didn't make it into the final database" even though it met her criteria).)

238 (*Id.* 177:23-25 ("Rosenblatt was included in the review" but "didn't make it into the final graph or the final group of ten").)

239 (*Id.* 178:14.)

240 (Diette Rep. at 17-18.) Dr. Smith-Bindman produced a spreadsheet of the data used in her analysis. (2-TalcDataResults-janehall.xlsx (attached as Ex. I1 to Tersigni Cert.).) It contains several tabs, one of which is labeled "All Papers" and another is labeled "ExcludingRosenblatt." Comparing the data between these two tabs shows that omitting Rosenblatt 2011 increased her odds ratio for regular use and HGSOC from 1.38 to 1.52 and for regular use and all ovarian cancer from 1.32 to 1.43. (*Id.*) That the spreadsheet contains separate tabs containing data analyses with and without Rosenblatt 2011 strongly indicates that the study's omission was calculated to produce higher odds ratios (contrary to how Dr. Smith-Bindman attempted to portray it at her deposition). Moreover, as Dr. Diette explains, Dr. Smith-Bindman's explanation that she omitted Rosenblatt 2011 because it did not affect her results makes no sense, since "all other things being equal, a more robust data set is obviously preferable." (Diette Rep. at 17.)

In addition, Dr. Smith-Bindman admittedly made no effort to assess the quality of the case-control studies in her review,[241] which is a problem because, as plaintiffs' experts acknowledge, a meta-analysis "should include a qualitative review of the individual studies," including "a risk of bias assessment, of which cofounding is – is one risk."[242] This is not merely a theoretical problem because only two of the 10 studies ultimately included in Dr. Smith-Bindman's analysis reported statistically significant findings.[243]

In short, Dr. Smith-Bindman's haphazard application of her own outcome-oriented selection criteria resulted in the inclusion only of studies supporting her hypothesis. Such a "conclusion-driven" approach, involving the "appli[cation of] [her] techniques inconsistently, without explanation, to different subsets of the body of evidence raises real issues of reliability." *Zoloft III*, 858 F.3d at 798; *see also, e.g.*, *Eghnayem v. Bos. Sci. Corp.*, 57 F. Supp. 3d 658, 688 (S.D. W. Va.

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241 (Smith-Bindman Rep. at 29.)

242 (Dep. of April Zambelli-Weiner, Ph.D. Vol. II 308:9-309:7, Feb. 7, 2019 (attached as Ex. B4 to Tersigni Cert.); *see also* Singh Rep. at 8 (in conducting a meta-analysis, an epidemiologist must "carefully examine the individual studies for their limitations and susceptibility to bias and confounding").)

243 (Smith-Bindman 2/7/19 Dep. 166:20-168:22.) Dr. Smith-Bindman's unprincipled approach also led to exclusion of particularly relevant data, such as studies regarding talc use on condoms and diaphragms (which introduce talc directly into the vagina). (Smith-Bindman Rep. at 32-33.) These omitted studies report no association between talc exposure and ovarian cancer. (Diette Rep. at 17.)

2014) (excluding experts who performed a "haphazard application of [their] tests" replete with "errors"; "***Vigorous adherence to protocols and controls are the hallmarks of 'good science***.'") (emphasis added) (citation omitted).

***Second***, Dr. Smith-Bindman's selection of studies that reported "regular talc use" was highly subjective and unrepeatable. *See, e.g.*, *In re TMI Litig.*, 193 F.3d at 703 n.144 (explaining that expert testimony based on a "subjective methodology" does not satisfy *Daubert* because "the only person capable of testing or falsifying the hypothesis is the creator of the methodology"); *In re Diet Drugs (Phentermine, Fenfluramine, Dexfenfluramine) Prods. Liab. Litig.*, No. MDL 1203, 2001 WL 454586, at *10, *13 (E.D. Pa. Feb. 1, 2001) (excluding experts in part because their methodologies were subjective and not capable of reproduction). As Dr. Smith-Bindman herself put it, she "tried to be consistent in defining exposure, but this factor was subjectively determined by the individual studies."[244]

Dr. Smith-Bindman arbitrarily chose to define "regular use" as "daily or at least more than 3 uses per week."[245] For unexplained reasons, she then vaguely broadened her definition of "regular use" so that she could also include studies that: (1) "defined use as 'regular' where the description made it clear that this was regular use"; (2) defined "regular use" "as at least once a month," but only if they

244 (Smith-Bindman Rep. at 34.)

245 (*Id.* at 32.)

"further characterized women into different categories of use," in which case she "included data for women in the highest use category as long as this . . . group was large enough to be meaningful"; or (3) "asked about ever use" but reported data that "may have reflected daily use."[246] This step in and of itself cannot be tested or repeated, as Dr. Smith-Bindman fails to explain how she determined, for example, that a study's "description made it clear" that it reported on (her arbitrary and evolving definition of) "regular use"; or that data from ever/never studies "may have reflected daily use"; or how large a subgroup had to be to be "meaningful." *See, e.g.*, *Snodgrass*, 2002 WL 485688, at *12-13 (excluding an expert whose "arbitrar[y]" "opinion d[id] not consist of a testable hypothesis," leaving it "doubtful that another expert could ascertain the same conclusion"); *see also Zoloft III*, 858 F.3d at 797 ("***[A]ny*** step that renders the analysis unreliable under the *Daubert* factors renders the expert's testimony inadmissible . . . .") (citation omitted).

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[246] (*Id.*) Dr. Smith-Bindman acknowledges that "[t]his measure of regular use is imprecise" but argues that it "is more accurate and meaningful than evaluating talcum powder exposure as any use." (*Id.*) But as explained in the text, Dr. Smith-Bindman's subjective and haphazard definition is the antithesis of "accurate." And her claim that her definition is more "meaningful" contradicts the opinion of her fellow plaintiffs' expert Dr. Siemiatycki, who explains that "[b]oth the qualitative metrics (ever/never) and quantitative metrics (a lot of use compared with a little use) are valid and useful." (Siemiatycki Rep. at 15.)

Moreover, Dr. Smith-Bindman's arbitrary definition of "regular use" enabled her to exclude studies that did not support her preconceived conclusion, i.e., that "regular" talc use is associated with an increased risk of HGSOC. Most notably, this includes Gates 2010, which defined "regular genital talc use" as use more than once per week, and would have dramatically decreased the odds ratio for HGSOC, since it found that the modest association with HGSOC reported in Gertig 2000 disappeared with ten additional years of study.[247] Gates 2010 would have met Dr. Smith-Bindman's criterion of defining "regular use" "as at least once a month" had she not inexplicably refined that criterion to require "further characteriz[ing] women into different categories of use."[248] Accordingly, it appears that Dr. Smith-Bindman manipulated impermissibly subjective criteria to exclude unfavorable evidence, further supporting the exclusion of her testimony. *See Snodgrass*, 2002 WL 485688, at *12 ("The subjective inclusion and exclusion of data suggest that Dr. Moshman manipulated the data to achieve a desired result. This weighs against the reliability of Dr. Moshman's methodology.").

***Third***, Dr. Smith-Bindman's meta-analysis was all the more unreliable because she used inaccurate data and unreliably estimated other data. *See Kim v. Crocs, Inc.*, No. 16-00460 JAO-KJM, 2019 WL 923879, at *8 (D. Haw. Feb. 25,

247 *See* Gates 2010 at 46, 50 & tbl. 40.

248 (*See* Smith-Bindman Rep. at 32.)

2019) (excluding expert's testimony because his opinion was based on inaccurate measurements; "it is unclear how sound and reliable opinions could be corroborated by data that [the expert] himself admits had a high rate of error"); *Dart v. Kitchen Bros. Mfg. Co.*, 253 F. App'x 395, 398-99 (5th Cir. 2007) (excluding expert partially because he relied on a different expert's miscalculations); *Wagner v. ABW Legacy Corp.*, No. CV-13-2245-PHX-JZB, 2016 WL 880371, at *8 (D. Ariz. Mar. 8, 2016) (excluding expert whose "calculations are admittedly based on numerous data entry errors"); *Castellow v. Chevron USA*, 97 F. Supp. 2d 780, 793 (S.D. Tex. 2000) (excluding expert in part because "the mathematical errors which required multiple amendments to his reports call into question the validity of his opinions"); *Robinson v. Sanctuary Record Grps., Ltd.*, 542 F. Supp. 2d 284, 292-93 (S.D.N.Y. 2008) (expert's opinion was "insufficiently reliable" because, among other things, "his calculations contained material errors such as double-counting"), *vacated on other grounds by Robinson v. Sanctuary Music*, 383 F. App'x 54 (2d Cir. 2010).

As Dr. Smith-Bindman was forced to concede at her deposition, her data abstraction was "not perfect" and contained numerous errors.[249] This is an understatement. In fact, ***none*** of the confidence intervals set forth in her report

[249] (Smith-Bindman 2/7/19 Dep. 104:22-105:21.)

matched those reported in the corresponding studies.[250] Moreover, Dr. Smith-Bindman also acknowledged that she may have double-counted individuals who were reported on by multiple studies[251] and that Dr. Hall was forced to "estimate" necessary variables that were not directly reported in the studies (most notably, the number of women in various subcategories).[252] These sorts of irregularities make

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[250] (*Id.* 182:13-183:24; *see also, e.g.*, Ballman Rep. at 42 (tables setting forth the differences between Smith-Bindman's data and that in the underlying studies).) Defendants agreed to Dr. Smith-Bindman's request to conduct her deposition over two days because she was recovering from a concussion. Dr. Smith-Bindman provided an explanation for the inaccurate confidence intervals only after inappropriately calling Dr. Hall the evening between her two deposition sessions for assistance answering questions about data inaccuracies and her methodology. (*See* Smith-Bindman 2/8/19 Dep. 254:9-17.) Her explanation – that Dr. Hall herself calculated the confidence intervals instead of using the intervals the studies reported (*id.* 256:6-13) – only illustrates that Dr. Smith-Bindman's entire analysis was an unverifiable "'black box' approach to" evaluating causation. *See Mirena*, 341 F. Supp. 3d at 248-49.

[251] (Smith-Bindman 2/8/19 Dep. 344:9-345:3.)

[252] (Smith-Bindman 2/7/19 Dep. 186:16-187:4 ("I would have told her, when the raw numbers for those missing proportions were not available, to do her best to estimate those."); *see also* Ballman Rep. at 41 (explaining that the "number of individuals in each group is needed to arrive at the weights that will be used when combining the reported risk ratios in the publications that are part of the meta-analysis").) Dr. Smith-Bindman produced a series of emails between her and Dr. Hall, including an exchange in which Dr. Hall proposed "do[ing] my best to estimate" data "[w]here the raw numbers are not available." (Email Correspondence between Rebecca Smith-Bindman, M.D., and Dr. Jane Hall, at 5 (Sept. 2018) (Smith-Bindman 2/7/19 Dep. Ex. 24) (attached as Ex. B41 to Tersigni Cert.).) Dr. Smith-Bindman did not produce a written response to this and numerous other issues, but her overall correspondence indicates that she did provide them, perhaps as a separate document that was not produced. (*See id.* at 4 (Dr. Hall writing: "Thanks for your responses!- they're very helpful.").) In any

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it impossible to rely on Dr. Smith-Bindman's work and further require exclusion of her opinions.[253] *See, e.g.*, *In re TMI Litig. Cases Consol. II*, 911 F. Supp. 775, 795-96 (M.D. Pa. 1996) (excluding expert because, among other things, "his use of speculation, assumptions and 'eyeballing' of figures, expose[d] [the expert's] methodology to a potentially high rate of error"); *Kim*, 2019 WL 923879, at *8 (excluding expert who admitted his data "had a high rate of error"); *see also Bracco*, 627 F. Supp. 2d at 451 (striking expert who used "incorrect" confidence intervals).

Dr. Smith-Bindman also admittedly did not apply the same rigor that she would have applied for a published paper.[254] Among other things, Dr. Smith-

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event, as noted in the text, Dr. Smith-Bindman confirmed in her deposition that she instructed Dr. Hall to go forward with estimating.

[253] Other parts of Dr. Smith-Bindman's report are replete with similar errors. For example, she suggests that a 2004 study failed to report an odds ratio (Smith-Bindman Rep. at 24, 30), even though the study clearly documents one, *see* Pike et al., *Hormonal Factors and the Risk of Invasive Ovarian Cancer: A Population-Based Case-Control Study*, 82(1) Fertility & Sterility 186 (2004) (attached as Ex. A114 to Tersigni Cert.) (reporting OR of 1.60 (95% CI 1.18-2.18)). In addition, she categorized Cramer's 2016 study as a pooled analysis (*see* Smith-Bindman Rep. at 24), even though Cramer classified it as a case-control study (*see* Saenz Rep. at 9-10 (documenting instances of incorrect information in Dr. Smith-Bindman's report)).

[254] (*See, e.g.*, Smith-Bindman 2/7/19 Dep. 77:14-18 (agreeing that she wrote in her email soliciting Dr. Hall "I am doing a review for a legal case and don't need quite the detail I would usually need for a paper") (quoting Smith-Bindman 2/7/19

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Bindman did not write down the protocol she followed in conducting her review;[255] nor did she document the assumptions she and Dr. Hall made in abstracting and analyzing data.[256] As Dr. Smith-Bindman was forced to admit, she would "include greater details about the methodology so that other investigators could duplicate [her] work" if she published it.[257] Dr. Smith-Bindman's omission of critical information and concession that her analysis does not meet the standards for peer review likewise show that it was unreliable. *See, e.g.*, *Burst*, 2015 WL 3755953, at *10, *14 ("The [c]ourt cannot credit Dr. Infante's calculations which involve calculating different results from separate data sets from this study without, at the very least, evidence of his calculations, let alone some indication of why this calculation is appropriate . . . ."); *cf., e.g.*, *Zoloft III*, 858 F.3d at 792 (factors guiding *Daubert* analyses include "the testability of the hypothesis, whether it has been peer reviewed or published, the error rate, [and] whether standards controlling the technique's operation exist").

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Dep. Ex. 16); *id.* 103:6-104:18 (Dr. Smith-Bindman omitted "certain details [in her report] that you would typically put in a journal article" because she did not think the reader "would be interested in some of those biostatistical nuances").)

255 (*Id.* 154:20-155:2.)

256 (*Id.* 197:19-198:6.)

257 (*Id.* 103:1-5.)

In short, Dr. Smith-Bindman's meta-analysis was conclusion-driven, unreplicable, error-ridden and generally unreliable. For this reason, too, her opinions should be excluded under *Daubert*.

## III. PLAINTIFFS' EXPERTS' OPINIONS ARE CONTRARY TO THE SCIENTIFIC CONSENSUS, AND DRS. SIEMIATYCKI AND MOORMAN'S OPINIONS ARE PARTICULARLY UNRELIABLE BECAUSE THEY CONTRADICT THEIR OWN PRE-LITIGATION PUBLICATIONS.

Plaintiffs' experts' general causation opinions should also be excluded because they are generally inconsistent with the scientific consensus that a causal relationship between talc use and ovarian cancer has not been established and because two of the experts' opinions contradict their own published writings.

***First***, in light of the discussion in Section I, it should come as no surprise that plaintiffs' experts' opinions are contrary to the scientific consensus. This separately requires their exclusion under *Daubert*. *See, e.g.*, *Norris v. Baxter Healthcare Corp.*, 397 F.3d 878, 885-86 (10th Cir. 2005) (excluding experts' opinions that were "flatly contrary to *all* of the available epidemiological evidence" and thus were "scientifically unreliable because they assume what science has largely shown does not exist"); *Rimbert v. Eli Lilly & Co.*, No. 06-0874 JCH/LFG, 2009 WL 2208570, at *13-14 (D.N.M. July 21, 2009) (excluding expert who sought to opine that Prozac can cause suicide, contrary to overwhelming scientific consensus, including the FDA, "numerous peer-reviewed publications on

controlled clinical trials, meta-analyses of controlled clinical trials, and other epidemiological studies," and who failed to adequately "account[] for any of the many contrary epidemiological studies"), *aff'd*, 647 F.3d 1247 (10th Cir. 2011); *Miller v. Pfizer, Inc.*, 196 F. Supp. 2d 1062, 1067, 1085 (D. Kan. 2002) (excluding expert whose "distinctly minority view" that Zoloft could cause suicide – which he attempted to support with a Bradford Hill-type analysis containing "glaring, overwhelming and unexplained" flaws – conflicted with the scientific consensus, including "[t]he American College of Neuropsychopharmacology, the FDA's PDAC, and the Medicines Control Agency in his own United Kingdom," all of which had "reached contrary conclusions"); *McMunn v. Babcock & Wilcox Power Generation Grp., Inc.*, No. 10-143 et al., 2013 WL 3487560, at *22 (W.D. Pa. July 12, 2013) (excluding expert whose opinion that uranium can cause cancer conflicted with public health conclusions, including by the UK Royal Society on the Health Hazards of Uranium and the UN Scientific Committee on the Effects of Atomic Radiation). As one court has explained, when a litigation expert brings a "distinct minority" view to the courtroom, it should "raise a red flag"; specifically, "[w]hen a scientist claims to rely on a method practiced by most scientists, yet presents conclusions that are shared by no other scientist, the [trial] court should be wary that the method has not been faithfully applied." *Motorola Inc. v. Murray*, 147 A.3d 751, 757-58 (D.C. 2016) (alterations in original) (citation omitted).

This is such a case. Numerous public health authorities that have studied the issue have reached the ***exact opposite conclusion*** as to any connection between talc and ovarian cancer as that espoused by plaintiffs' experts here. The FDA reviewed the relevant body of scientific literature in 2014 and "***did not find that the data submitted presented conclusive evidence of a causal association between talc use in the perineal area and ovarian cancer***."[258] Similarly, NCI has repeatedly reiterated its conclusion that the "weight of the evidence ***does not support an association***" between talc use and increased ovarian cancer risk.[259] And IARC concluded that talc is only "possibly carcinogenic" to humans.[260] Finally, in March of this year, a review article in the New England Journal of Medicine identified risk factors for mucinous and serous ovarian cancer and ***did not list talc***.[261]

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[258] FDA Denial Letter at 1 (emphasis added).

[259] *See, e.g.*, 2019 NCI PDQ (emphasis added).

[260] IARC 2010 Monograph at 412. IARC classifies talc as a "Group 2B" agent that is "possibly carcinogenic" to humans, which means there is ***"limited" evidence of carcinogenicity***. This is the same category into which it has placed pickled vegetables, ginkgo biloba, and aloe vera whole leaf extract. *See* IARC 2010 Monograph at 412.

[261] Morice 2019 at 1257 tbl. 1; *see also* World Cancer Res. Fund Int'l Continuous Update Project, *Diet, Nutrition, Physical Activity and Ovarian Cancer* (revised 2018) (attached as Ex. A154 to Tersigni Cert.) (review by Dr. McTiernan's panel not listing talc use as a risk factor for ovarian cancer). As explained in Dr. Mossman's report, The New England Journal of Medicine has the *(cont'd)*

Defendants anticipate that plaintiffs will point to the recent Health Canada Draft Screening Assessment as supportive of their views, but any such attempt would be self-defeating.[262] For one thing, Health Canada stated in the draft screening assessment that the body of talc literature does ***not*** establish causation, classifying talc use as only a "***potential concern*** for human health."[263] In reaching this conclusion, Health Canada observed that "the etiology of most ovarian tumors, in general, has not been well established."[264] Plaintiffs' counsel have highlighted isolated statements in the Health Canada Draft Screening Assessment during depositions, including portions noting that "meta-analyses of the available human

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highest "impact factor" of any journal, which essentially means that it is the most prestigious journal. (Mossman Rep. at 5.)

[262] The Health Canada Draft Screening Assessment post-dated plaintiffs' experts' reports and is accordingly not cited, but plaintiffs' experts have testified that they believe it supports their opinions (*e.g.*, McTiernan Dep. 204:7-12 (it "substantiate[s] [her] opinion"); Clarke-Pearson Dep. 301:14-18 (it "only supports my opinion"); Siemiatycki Dep. 84:9-15 ("I would say that the Health Canada report reinforces the notion that this issue is becoming a front burner issue for public health agencies. But it -- since I didn't explicitly address that I would say it doesn't change anything that's in my report."); Singh Dep. 96:18-24 (stating that she did not "rely[] on" the Health Canada Assessment but "their methodology . . . and opinions are consistent with mine"); Carson Dep. 89:10-19 (stating the Health Canada draft screening assessment "support[ed his] conclusions")), and defendants expect that they will rely on it extensively at the *Daubert* hearing.

[263] Draft Screening Assessment at 28 (emphasis added); *see also* Taher 2018 at 2 (concluding that "[p]erineal use of talc powder is a ***possible*** cause of human ovarian cancer") (emphasis added).

[264] Draft Screening Assessment at 18.

studies in the peer-reviewed literature indicate a consistent and statistically significant positive association between perineal exposure to talc and ovarian cancer" and that "available data are indicative of a causal effect."[265] But the Health Canada Draft Screening Assessment ultimately ***declines*** to find a causal relationship between talcum powder exposure and ovarian cancer, consistent with the findings of various other governmental agencies.[266]

It also deserves emphasis that the Health Canada Draft Screening Assessment is an example of a regulator taking a precautionary approach with respect to public health – not a scientific conclusion about causation. As courts have recognized, a regulatory agency's "prevention-oriented" standards are "materially different" from the standard that must be applied under *Daubert*. *In re Zicam Cold Remedy Mktg., Sales Practices, & Prods. Liab. Litig.*, No. 09-md-2096-PHX-FJM, 2011 WL 798898, at *10 (D. Ariz. Feb. 24, 2011); *see also Glastetter*, 252 F.3d at 991 (government agencies employ a preventative perspective that is aimed at reducing public exposure, which requires a lesser showing of harm than the preponderance-of-the-evidence standard); *Rider v. Sandoz Pharm. Corp.*, 295 F.3d 1194, 1201 (11th Cir. 2002) (explaining that regulatory agencies employ a risk-utility analysis that is distinct from the scientific

265 *Id.* at iii.

266 *See* IARC 2010 Monograph at 412; 2019 NCI PDQ; FDA Denial Letter at 1.

standard demanded by a court, which is "required by the *Daubert* trilogy to engage in objective review of evidence to determine whether it has sufficient scientific basis to be considered reliable"). Indeed, Health Canada has elsewhere explained that in performing risk assessments, it applies "[p]recaution . . . to avoid the potential underestimation of risk due to a lack of information, thus ***erring on the side of being protective of human health*** and the environment."[267] It is all the more telling that as a regulatory agency explicitly erring on the side of caution, Health Canada nevertheless stopped short of embracing a causal connection between talc and ovarian cancer.

***Second***, Drs. Siemiatycki and Moorman's causation opinions contradict the views they published about talc and ovarian cancer prior to becoming plaintiffs' experts. This two-faced approach to causation is a strong indication that these experts have not "employ[ed] in the courtroom the same level of intellectual rigor that characterizes the practice of an expert in the relevant field." *Kumho Tire Co. v. Carmichael*, 526 U.S. 137, 152 (1999); *see also, e.g.*, *Schepise*, 1997 WL 897676, at *17 (excluding expert who had "not tested her theory . . . anywhere outside of

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[267] Health Canada, *Application of Weight of Evidence and Precaution in Risk Assessment* (last updated June 15, 2017) (emphasis added), https://www.canada.ca/en/health-canada/services/chemical-substances/fact-sheets/application-weight-of-evidence-precaution-risk-assessments.html (attached as Ex. A57 to Tersigni Cert.).

the judicial arena"); *Lust ex rel. Lust v. Merrell Dow Pharm., Inc.*, 89 F.3d 594, 597 (9th Cir. 1996) (rejecting expert testimony as unreliable where the expert "published the 1984 article . . . [when] he was at that time already a professional plaintiff's witness" because "[i]t [wa]s not unreasonable to presume that [the expert]'s opinion . . . was influenced by a litigation-driven financial incentive"); *Johnson v. Manitowoc Boom Trucks, Inc.*, 484 F.3d 426, 435 (6th Cir. 2007) (explaining that a high degree of scrutiny should be applied to experts whose "opinions were conceived, executed, and invented solely in the context of . . . litigation") (citation omitted). Indeed, courts are especially skeptical of experts who adopt litigation opinions that contradict their prior published views. *See, e.g.*, *In re Fosamax Prods. Liab. Litig.*, No. 1:06-md-1789 (JFK), 2009 WL 2878439, at *5 (S.D.N.Y., Sept. 9, 2009) (excluding opinion of general causation expert that was contrary to his academic publications; reversal of expert's opinion "raises a question as to whether it was made independent of litigation concerns"); *Zoloft I*, 26 F. Supp. 3d at 460 (excluding opinion that SSRIs as a class have teratogenic effects because it "is directly contrary to the findings of her own peer-reviewed, published research"); *Fireman's Fund Ins. Co.*, 394 F.3d at 1059 (noting that a "sudden reversal of opinion . . . seriously undermines the reliability of" an expert's opinion).

Here, Dr. Siemiatycki ***chaired*** the IARC working group that found only "*limited evidence*" of an association between talc and ovarian cancer[268] and wrote in 2008 that the "current body of experimental and epidemiological evidence is ***insufficient to establish a causal association*** between perineal use of talc and ovarian cancer risk."[269] Moreover, although Dr. Moorman has researched ovarian cancer for decades, she has rarely, if ever, listed perineal talc use as a risk factor.[270] And both times Dr. Moorman investigated whether talc use is associated with ovarian cancer prior to becoming a plaintiffs' expert in 2016, she found no statistically significant association and wrote that neither ovarian cancer nor peritoneal cancer "was found to be associated with talc use."[271] In addition, to the

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[268] (Siemiatycki Dep. 136:14-19, 144:6-15.)

[269] Langseth 2008 at 359 (emphasis added).

[270] *See* Terry et al., *Supplemental Selenium May Decrease Ovarian Cancer Risk in African-American Women*, 147 J. Nutrition 621, 623-24 (2017) (attached as Ex. A140 to Tersigni Cert.); Peres et al., *Analgesic Medication Use and Risk of Epithelial Ovarian Cancer in African - American Women*, 114 Br J Cancer 819, 823 (2016) (attached as Ex. A110 to Tersigni Cert.); Qin et al., *Dietary Quality and Ovarian Cancer Risk in African-American Women*, 185 J. Epidemiology 1281, 1286-87 (2017) (attached as Ex. A115 to Tersigni Cert.); Alberg et al., *Socioeconomic Status in Relation to the Risk of Ovarian Cancer in African-American Women: A Population-Based Case-Control Study*, 184 J. Epidemiology 274, 278-79 (2016) (attached as Ex. A6 to Tersigni Cert.); *see also* Moorman *Ingham* Dep. 148:9-18, 149:14-150:24, 153:6-22, 154:18-155:24, 156:5-13, 181:10-25.

[271] *See* Grant et al., *Primary Peritoneal and Ovarian Cancers: An Epidemiological Comparative Analysis*, 21 Cancer Causes Control 991, 996 (2010) *(cont'd)*

extent Dr. Moorman has found that talc use is (weakly) associated with ovarian cancer in the studies she has published since becoming a plaintiffs' expert, she has made clear that her current position that talc use ***causes*** ovarian cancer is a litigation opinion that she would not espouse in her scientific work.[272] In any event, those studies cannot support her methodology here because she may have been "influenced by a litigation-driven financial incentive" when publishing them – a conflict of interest she failed to disclose to one of the journals until after her deposition as a plaintiffs' expert. *See Lust*, 89 F.3d at 597 (rejecting expert testimony as unreliable where expert "published the 1984 article . . . [when] he was at that time already a professional plaintiff's witness").[273]

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(attached as Ex. A50 to Tersigni Cert.); Moorman 2009 at 601-02. (*See* Moorman Dep. 126:12-137:10, 138:13-15 (admitting that in her 2009 study she found "little evidence of an association [between talc and ovarian cancer]"); *id.* 138:21-140:18 (reporting a "not statistically significant association" for talc and ovarian cancer in the 2010 study she co-authored).)

[272] (*See* Moorman Dep. 166:9-167:6 (stating "that epidemiologists are frequently loath[] – or don't often use the word 'causal'"), 182:9-16 (stating it is "epi 101[] that everything that is associated is not necessarily a cause"); Moorman *Ingham* Dep. 122:14-124:9, 127:2-8, 208:18-209:4 (testifying that she never espoused causation opinion outside the litigation context).)

[273] (*See also* Moorman Dep. 21:2-17, 22:3-25.) Dr. McTiernan's work as a WCRF panelist is similarly contrary to her litigation views. As noted above, her WCRF panel did ***not*** include talcum powder as an established cause of ovarian cancer in its 2014 report. (McTiernan Dep. 78:16-80:12.) Further, the WCRF has published on its website that "there is not enough evidence to be certain" of the

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Neither Dr. Siemiatycki nor Dr. Moorman has adequately explained these changes of heart. Dr. Siemiatycki claims that, since the IARC evaluation in 2006 there has been new research on epidemiology and possible mechanisms,[274] but he ultimately conceded that he has no idea whether a new review of the available evidence would lead to a different result.[275] In fact, the epidemiological evidence has weakened over recent years, making it even less likely that IARC would embrace Dr. Siemiatycki's litigation opinions. Most notably, since 2006, there have been three large-scale cohort studies that failed to find an association between

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"link between talcum powder, talc, and ovarian cancer," and that "[e]ven if there were an increased risk, scientists estimate it ***would be small***." (*Id.* 101:5-14 (emphasis added).) Dr. McTiernan recently provided essentially the same causation opinion that she offers here in testimony before Congress. However, Dr. McTiernan's testimony occurred after she was retained as a plaintiffs' expert and merely parroted her expert report in this matter. Thus, Dr. McTiernan's unpublished testimony was also clearly "influenced by a litigation-driven financial incentive." *Lust*, 89 F.3d at 597. The same goes for correspondence she and Dr. Siemiatycki wrote to Health Canada after they completed their depositions, essentially summarizing their litigation opinions. (*See* Email Submission of Anne McTiernan, M.D., Ph.D. to Health Canada, Feb. 5, 2019 (attached as Ex. F1 to Tersigni Cert.); Email Exchange between Anne McTiernan, M.D., Ph.D. and Scott Hancock, Health Canada, Feb. 21, 2019 (attached as Ex. F3 to Tersigni Cert.); Letter from Jack Siemiatycki, M.Sc., Ph.D. to Health Canada, Feb. 6, 2019 (attached as Ex. F2 to Tersigni Cert.); Email Exchange between Jack Siemiatycki, M.Sc., Ph.D. and Scott Hancock, Health Canada, Mar. 2019 (attached as Ex. F5 to Tersigni Cert.).)

274 (*See* Siemiatycki Dep. 142:15-143:16.)

275 (*See id.* 143:1-2.)

perineal talc use and ovarian cancer.[276] And Dr. Siemiatycki conceded at his deposition that the overall magnitude of the association has ***decreased*** as more evidence has accumulated.[277] While Dr. Siemiatycki claims that new evidence of dose-response between talc and ovarian cancer supports his opinions, the "primary" new evidence he cites is Terry (2013), which, as discussed above, ***did not*** find a dose response.[278]

Dr. Moorman, for her part, cannot point to any particular studies that prompted her to change her mind on causation, instead evasively referring to "a growing body of evidence" and admitting that she "would be hard-pressed to say" when she decided "there [was] enough evidence" to support her current causation opinions.[279]

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276 *See* Gates 2010; Houghton 2014; Gonzalez 2016.

277 (Siemiatycki Dep. 149:14-150:3 (admitting that the collective 1.28 odds ratio he calculates in his report is lower than the 1.35 relative risk published in the 2008 Langseth article); Berge 2018 at 6 ("in our cumulative meta-analysis we confirmed the trend toward lower overall risk estimates as more evidence accumulated").) This is also further evidence that plaintiffs' witnesses employed a "flawed methodology" by placing significant weight on the purported strength of any association between talc and ovarian cancer. *J.M. v. Sec'y of Health & Human Servs.*, No. 02-10V, 2018 WL 1514433, at *9 (Fed. Cl. Feb. 13, 2018) (reducing expert rate where his "flawed methodology" was "contradict[ed] [by] the most current epidemiology studies and other established medical science").

278 (*See* Siemiatycki Dep. 266:8-12.)

279 (Moorman Dep. 178:12-20.)

In short, Drs. Siemiatycki and Moorman's opinions are particularly suspect because they contradict opinions that these experts have subjected to peer review. This makes clear that "what's going on here is not science at all, but litigation." *Rutigliano v. Valley Bus. Forms*, 929 F. Supp. 779, 786 (D.N.J. 1996) (citation omitted).

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Plaintiffs' experts' opinions boil down to the notion that they know better than science – and that the Court should embrace hypotheses that are not supported by the current scientific literature. But as courts have repeatedly recognized, "[t]he courtroom is not the place for scientific guesswork, even of the inspired sort. Law lags science; it does not lead it." *E.g.*, *Perry*, 564 F. Supp. 2d at 468-69 (quoting *Rosen v. Ciba-Geigy Corp.*, 78 F.3d 316, 319 (7th Cir. 1996)) (rejecting causation opinion where, "[b]ased on the data that exist today . . . any link that plaintiffs' experts draw between [the agent and disease at issue] is mere guesswork—educated guesswork, but guesswork nonetheless"; "While such speculation is appropriate in the laboratory where a hypothesis can be tested by experiment, it has no place in the courtroom where no such testing is possible."). As such, "where no adequate study shows the link between a substance and a disease, expert testimony will generally be inadmissible, even if there are hints in the data that some link might exist." *Id.* at 468. Because plaintiffs' experts' causation opinions amount to

nothing more than "guesswork," they should be excluded from the courtroom to avoid "crippling verdicts on the basis of slender scientific evidence." *Id* at 468-69.

## CONCLUSION

For the reasons set forth above, the Court should exclude: (1) the entire opinions of Drs. Carson, Clarke-Pearson, Kane, McTiernan, Moorman, Siemiatycki, Singh, Smith-Bindman, Smith and Wolf; and (2) the portions of the opinions of Dr. Plunkett identified in footnote 1, *supra*.

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